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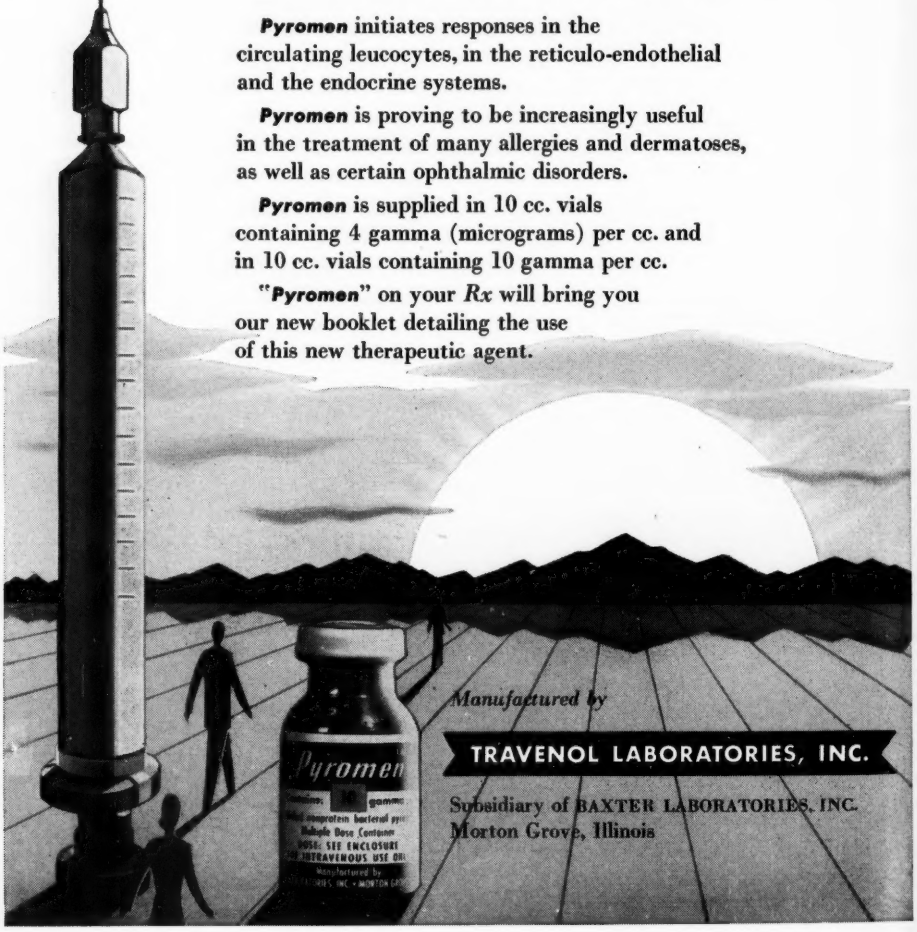

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GYNECOLOGY AND OBSTETRICS

LUME 94 APRIL, 1952 NUMBER 4

VALUE OF PEROPERATIVE MANOMETRIC AND ROENTGENOGRAPHIC EXAMINATION IN THE DIAGNOSIS OF PATHOLOGIC CHANGES AND FUNCTIONAL DISTURBANCES OF THE BILIARY TRACT

P. MALLET-GUY, M.D., Lyons, France

As long as surgery of the biliary tract is based solely on clinical data and visual and manual findings at operation, the results too often will be imperfect, and there will be a high percentage of recurrences. These recurrences are not due to technical errors alone, although any cholecystectomy may leave unrecognized an anatomical or functional obstruction of the common bile duct or an obstruction, which may produce a fistula. Even after choledochotomy, thorough catheterization will not establish the fact that the biliary tract is free of obstruction. With the exception of stones and other similar surgical lesions of the gallbladder and the common duct, there are other biliary syndromes which are not improved by medical treatment and which present a difficult problem for the surgeon. They constitute the static gallbladder which should not be treated routinely by the usual cholecystectomy.

In 1930, Mirizzi, fully aware of the imperfections of biliary surgery, advocated peroperative cholangiography. However, it is often difficult to interpret such cholangiograms without a fluoroscopic examination which is out of place and quite impossible to perform in an operating room. It seemed possible to me to substitute a manometric recording, ascribing to the curves of the biliary pressures the equivalent of fluoroscopic visualization.

Since 1942, a technique of peroperative manometric and roentgenographic examination of the biliary tract has been gradually perfected and simplified. In 1947, observations upon 550 cases were collected. By September 22, 1951, 1,500 operations on humans had been performed as well as extensive experiments on dogs. The method is by no means to be used only for a few selected cases, but when applied in a systematic way, it enables the surgeon to discover some unexpected facts, even if the case appears to be quite simple. It is essential that the technique be simple and that it not make the surgical procedure more complicated or longer than is necessary. It is essential, too, that as far as possible all factors of error should be eliminated.

General anesthesia, with nitrous oxide-ether-oxygen, does not disturb the functional status of the biliary tract if it is induced without premedication or complementary medication and without curarization. This became apparent after a few surgical observations and was corroborated by various experiments.

The technique comprises two successive and independent steps: (1) a manometric record-

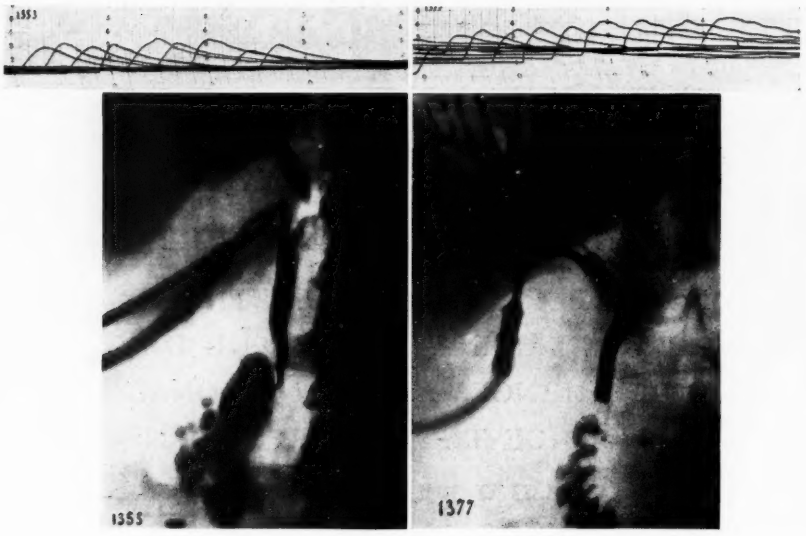

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Fig. 1. Stones in the gallbladder. Manometric and roentgenographic examination of the common duct during cholecystectomy. a, Case 1353. The gallbladder is normal, transcystic pressure 10 to 12 centimeters of water. Cholecystectomy without drainage. b, Case 1377. A stone of the ampulla of Vater is detected, transcystic pressure 18 centimeters of water.

ing for a hyperpressure test by injecting an isotonic and isothermic saline (NaCl) solution into the gallbladder or the common duct; (2) cholangiography, including 2 or 3 roentgenograms, taken at intervals of 3 minutes, after injection of a contrast fluid. Thus, the two methods check each other. Being independent, they do not have the same possibilities of error. If a discrepancy appears, it is possible to trace the disturbing factor which may have produced the false results. On the other hand, clinical and experimental observations (2) have proved that any measure of pressure produced by injecting a contrast fluid in the biliary tract cannot be carried out without some error. Among the hydrosoluble products, methane iodine by-products generally produce an artificial hypertension by creating a spasmodic reaction of the biliary ducts; oxypyridine iodine by-products (diodrast) also disturb the biliary pressure, either up or down. It is impossible to know beforehand the degree or even the direction of the reaction. Those reactions do not disappear quickly and may be the cause of error in manometric examinations which might be done afterward. As for the liposoluble iodine products, they are too oily to be used for manometric studies.

In the interpretation of cholangiograms one must take into account the disturbances thus produced in the functional state of the biliary tract. The manometric graphs may not verify the roentgenograms. The basic conditions of the recording must always be similar. Capillarity, in particular, is avoided by the use of trocars of an inner diameter of 2.5 millimeters. The curve of the hyperpressure test is recorded on a cylinder, running at one revolution each 25 seconds. Several successive graphs will establish the base level of the biliary pressure.

Experiments have confirmed the fact that the technique of manometric recording does not cause a reaction of the biliary ducts, even when done after repeated hyperpressure tests. The ascending part of the hyperpressure curve in reality indicates a slight increase of pressure in the biliary ducts. The upper part of the

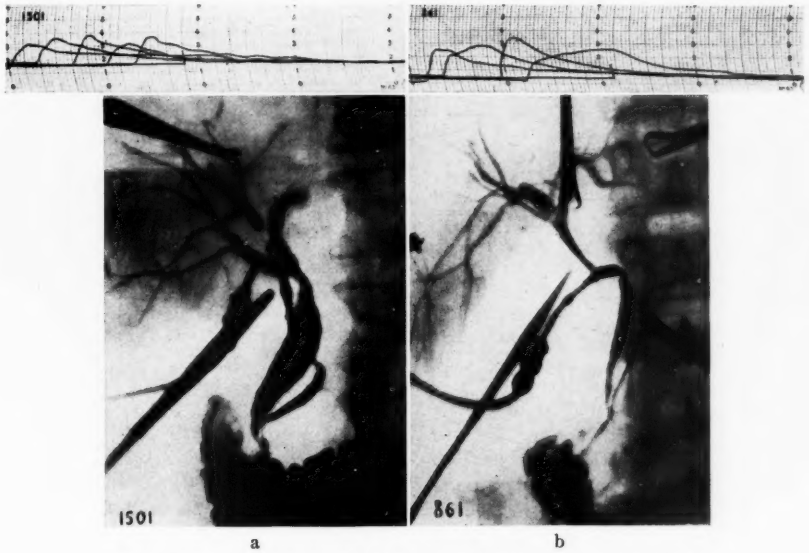

Fig. 2. Stones in the gallbladder. Manometric and roentgenographic examination of the common duct during cholecystectomy. a, Case 1501. Disease of the sphincter of Oddi, transcystic pressure 16 centimeters of water, dilatation of the common duct, reflux in Wirsung's duct. Vagotomy or transduodenal sphincterotomy is also indicated. b, Case 861. Hypotonia of the common duct and the sphincter of Oddi, pressure 2 to 4 centimeters of water, reflux in Wirsung's duct. Right splanchnicectomy is also indicated.

curve is made by the pressure in the system of joints and tubes.

The prime requisite for systematic manometric and roentgenographic peroperative examinations of the biliary tract is that the results be easily read and interpreted. The surgeon may only have a few minutes to confirm his diagnosis and take the necessary steps. Therefore, the manometric and roentgenographic examinations should be as simple, short and standardized as possible. In a way, the problem presents itself as a physiopathological biopsy, the indications of which are composed of the clinical data, the previous, or immediate, laboratory examinations, and, lastly, the surgical operation under different conditions according to the disease.

TECHNIQUE OF EXAMINATIONS PERFORMED DURING CHOLECYSTECTOMY

The simplest case in question is an ordinary cholecystectomy for gallstones, without common duct symptoms. The common duct and the pancreas are as carefully explored as if no other examination were contemplated. The exploration is usually a negative one, except that in some cases there is a slight inflammatory reaction of the pancreatic head. The cystic duct is searched for and identified. Half its circumference is cut beyond the point where the last stone has been located, and, as a rule, this is done 4 or 5 millimeters in front of the common duct. The cystic duct is never totally obstructed, but is likely to be dilated. It will be possible then to introduce a bent cannula which will be inserted into the common bile duct. During the first step of the operation, the nurse prepares the manometric apparatus, sets it at the zero point and checks the tightness of the joints. A series of hyperpressure tests may show: (1) a tracing which regularly stabilizes at 10 or 12 centimeters of water, which indicates a normal biliary passage (normal range 8 to 14 cm. of water); (2) a

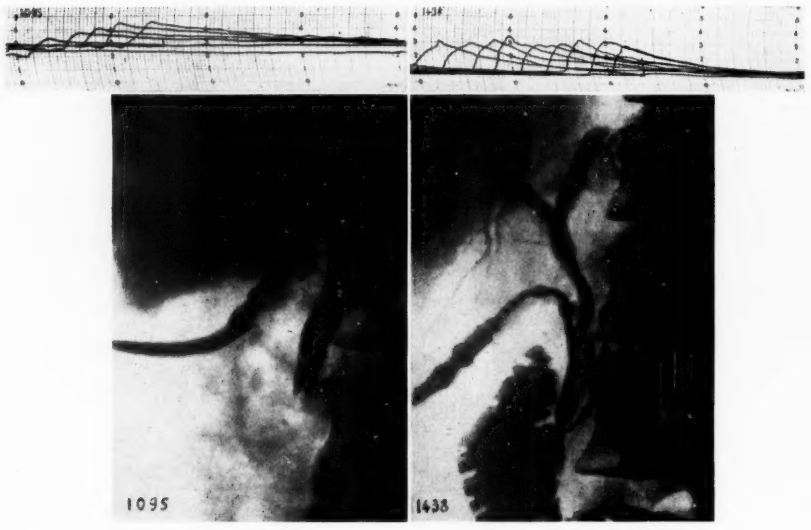

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Fig. 3. Recurrence after cholecystectomy. Manometric and roentgenographic examination during reoperation. a, Case 1095. A stone in the ampulla of Vater, pressure 18 centimeters of water. b, Case 1438. Hypotonia of the common duct, pressure 6 centimeters of water, reflux in Wirsung's duct. No drainage. Primary suture of the common duct. Right splanchnicectomy is indicated.

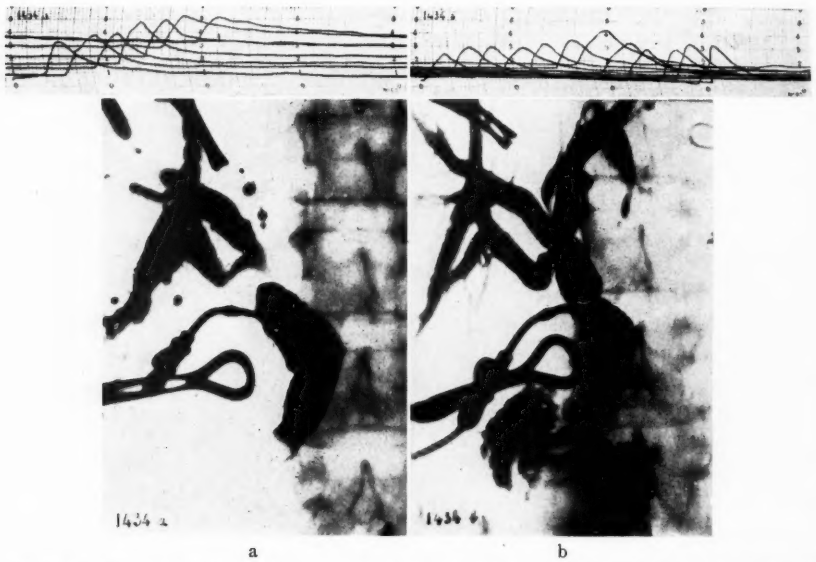

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Fig. 4. Stones in the common duct. Manometric and roentgenographic peroperative examination. a, A stone in the ampulla of Vater is detected; manometric curves at 33 centimeters of water. b, After extraction of the stone the pressure is stopped at about 8 centimeters of water; primary suture of common duct may be possible.

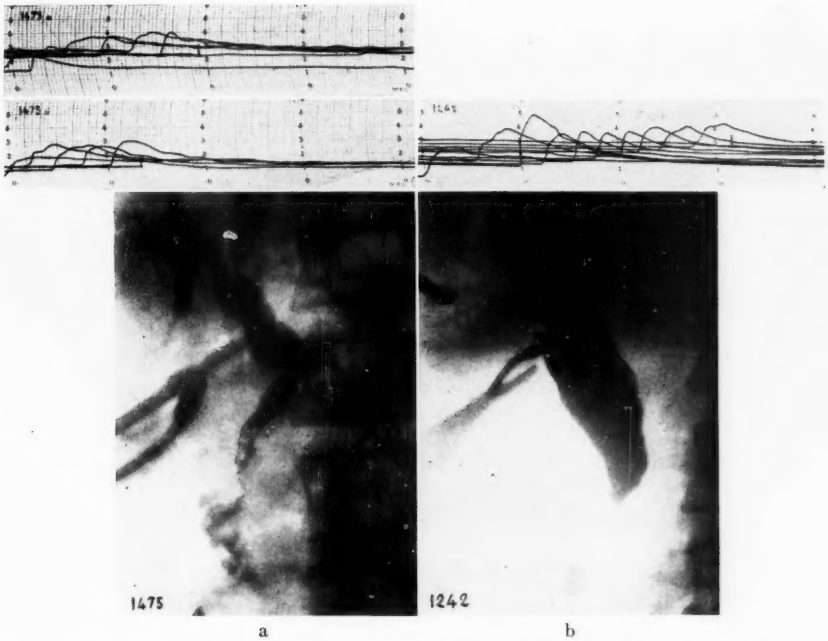

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Fig. 5. Stones in the common duct. Manometric and roentgenographic peroperative examination. a, Case 1475. After extraction of 7 stones by choledochotomy the pressure in the common duct remained constantly at 23 centimeters of water and the roentgenograms show 3 new undetected stones. b, Case 1242. After extraction of the stones by choledochotomy, there is still an obstruction. Pressure in the common duct, 29 centimeters of water, roentgenograms showing disease of the sphincter of Oddi; indication for a choledochoduodenostomy.

low tracing, below 7 centimeters of water, which suggests the existence of a hypotonia of the sphincter of Oddi; or, (3) a tracing stabilized at a high level, which indicates the presence of an obstruction until now unrecognized.

Then, the cholangiographic examination is performed. The first roentgenogram is taken after an injection of 10 cubic centimeters of iodized oil, a second 3 minutes later, and a third one, if need be, 3 minutes later without reinjection. If there has been no source of error, such as leaking or blocking up of the transcystic cannula, different manometric results will correspond with roentgenographic images typical of a normal biliary passage, of an obvious hypotonia of the sphincter of Oddi and of the common bile duct, or an obstruction such as: a small unrecognized, silent stone in the common duct; a relative compression by chronic pancreatitis; or, disease of the sphincter of Oddi, either a simple hypertonia or a fibrous narrowing.

If these diverse pathological conditions are not recognized, they will produce postoperative recurrences of pain or jaundice. Their frequency emphasizes the diagnostic value of manometric and roentgenographic examinations in the course of cholecystectomy. From August 9, 1950 to September 22, 1951, 100 cases of gallstones which were clinically and surgically free of complications were studied. In 38 per cent, there was another pathological condition as follows.

Normal common bile duct	62
Hypotonia of the common bile duct	14
Stone in the common bile duct	10*
Compression due to pancreatitis	3
Disease of the sphincter of Oddi	11
	100

*In 1942, R. Koppes and I collected 142 cases of stones of the gallbladder 15 with stones in the common duct, which had escaped observation and which were discovered by manometric and roentgenographic peroperative examination, i.e. 10.5 per cent.

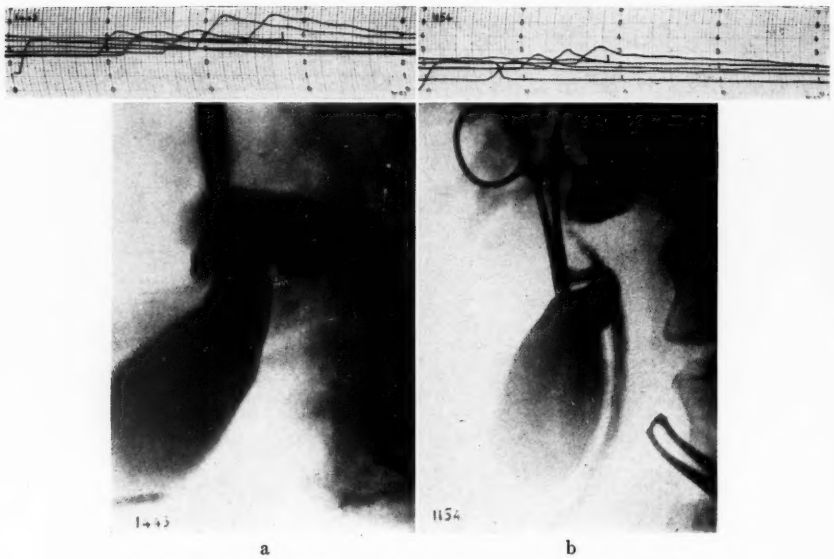

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Fig. 6. Strictures of biliary tract by malignant tumor. Manometric and roentgenographic peroperative examination. a, Case 1443. Stricture of the common duct by neoplasm of the head of the pancreas. The manometric curves by puncture of the gallbladder are higher and higher. b, Case 1154. Tumor of the left branch of the hepatic duct. Pressure in the gallbladder is normal, about 20 centimeters of water. Roentgenograms showing normal gallbladder and common duct but a dilated left branch of the hepatic duct.

MANOMETRIC AND ROENTGENOGRAPHIC EXAMINATION IN CASES OF RECURRENCE

In 1949, statistics concerning 58 reoperations after cholecystectomy were presented. The different factors, which may be revealed by manometric and roentgenographic examinations in the very course of cholecystectomy, were found with the same frequency. Technically, and this is a somewhat peculiar point, it is enough to search for the stump without dissecting any more, and then to place a cannula into the common duct. So, at the very first, necessary information is available on the anatomical or functional state of the common duct (Fig. 3). Thus an exploratory operation on the common duct will often be avoided, particularly if the recurrence is caused only by dystonia of the sphincter.

Stones in the common duct. When the clinical and operative findings have led to a definite diagnosis of stones in the common duct, manometric and roentgenographic examinations are performed only after choledochotomy, after the stones have been removed and the common duct freed. In this way, it may be possible to show that no other obstruction remains in the common duct (Figs. 4 and 5), and, after removal of the drain, that no fistula or recurrence will take place. These conditions will warrant proceeding with closure of the duct. When the cystic duct is widely dilated and allows exploration up and down the common duct, it is easy to put a bent cannula in place and fix it by ligation. When the duct has been opened for instrumental exploration, it is necessary to suture the wall of the common duct around a temporary tube (Kehr's drain or, better, a Pezzar cannula).

In a later series of 100 patients with stones in the common duct who were operated on between November 16, 1948 and September 22, 1951, manometric and roentgenographic reexaminations after choledochotomy showed

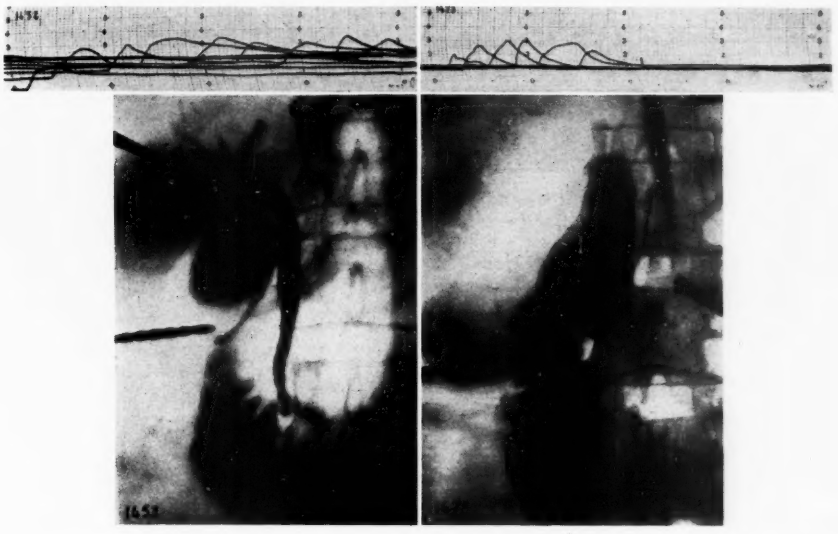

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Fig. 7. Manometric and roentgenographic examination by puncture of the gallbladder demonstrates a static gallbladder. a, Case 1452. The common duct is normal, pressure in the gallbladder is about 20 centimeters of water. b, Case 1478. Idiopathic hypotonia of the biliary tract, pressure in the gallbladder 10 centimeters of water. No cholecystectomy. Indication for right splanchnicectomy.

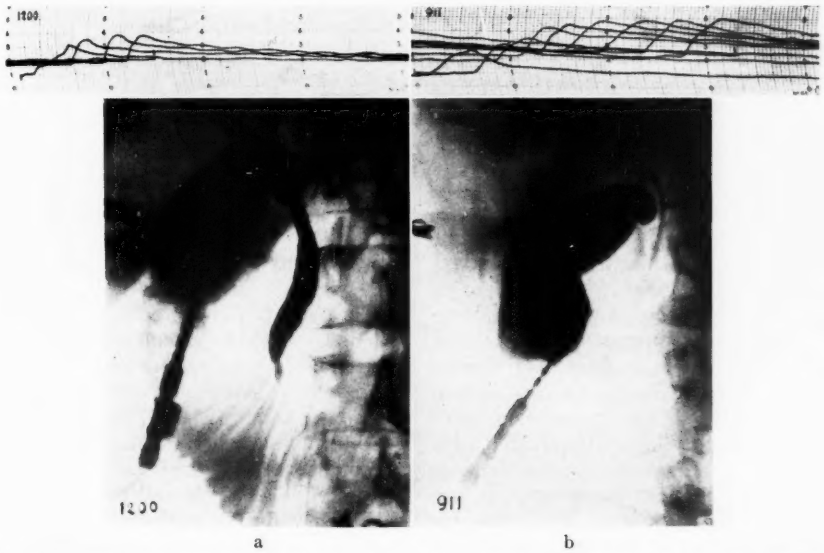

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Fig. 8. Manometric and roentgenographic examination by puncture of the gallbladder, static gallbladder. a, Case 1200. Idiopathic disease of the sphincter of Oddi. Pressure in gallbladder is nearly normal but the contraction of the common duct on the roentgenograms is demonstrative. Indication for vagotomy or transduodenal sphincterotomy. b, Case 911. Disease of the cystic duct, pressure in gallbladder 25 centimeters of water. On the roentgenograms very small evacuation of the gallbladder. Indication for cholecystectomy.

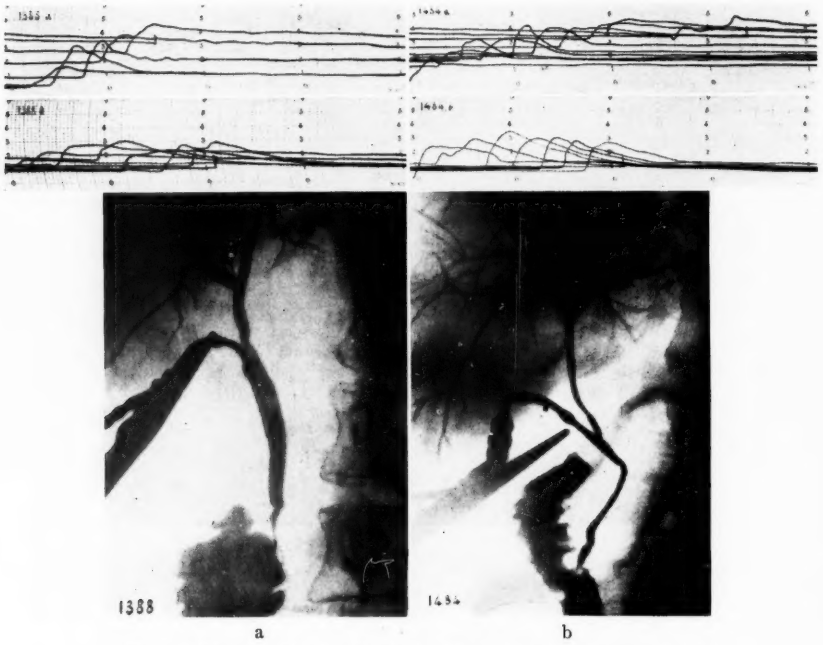

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Fig. 9. Disease of the cystic duct. Measurement of pressure in the gallbladder (upper tracings) gives "obstruction curves" which confirm the data of the preoperative cholecystography. Catheterization of the cystic duct will indicate the functional status of the common duct (lower tracings). a, Case 1388. Transcystic pressure 8 to 10 centimeters of water, normal roentgenogram. Cholecystectomy without drainage. b, Case 1434. The pressure is also normal, 9 centimeters of water, but the common duct seems to be abnormally contracted. After cholecystectomy a preventive vagotomy is indicated.

54 biliary ducts absolutely free; 12 with stones, or fragments of stones, undetected at the time of the last catheterization; 22 hypertonic reactions of the sphincter of Oddi, some of which are probably secondary to the instrumental trauma; 2 compressions by chronic pancreatitis, and 5 noncalculous obstructions not accurately identified. If we except certain hypertonic reactions of the sphincter of Oddi which would probably have disappeared with prolonged external drainage, we see that before manometric and roentgenographic examinations were used there was still a cause for fistula or postoperative recurrence, which we are now able to prevent. Thus we can decide when external drainage is required, or primary suture of the common duct (4), or a choledochoduodenostomy.

MANOMETRIC AND ROENTGENOGRAPHIC EXAMINATION THROUGH THE GALLBLADDER

Manometry and roentgenography of the biliary ducts are performed through the medium of a puncture of the gallbladder, whenever a cholecystectomy does not seem justified. This procedure should be followed: First, when the common duct is occluded by a malignant tumor (Fig. 6). In this instance, the method enables one to make a diagnosis if the tumor is located at the head of the pancreas or the ampulla of Vater and to determine if the gallbladder can be used for anastomosis, or if the hepatic duct must be used. Secondly, when jaundice is present, the cause of which is not found by surgical exploration, it may be a tumor of the hepatic bifurcation or of one of its branches, which the cholangiography

visualizes (Fig. 6), or hepatitis, for which it is important to know the functional status of the common bile duct. Third, when a syndrome of static gallbladder is present, the physiological pathology of such a condition is quickly analyzed by manometric and roentgenographic examinations.

Usually, the pressure in the gallbladder is about 18 centimeters of water (Fig. 7). In hypotonia of the biliary ducts, pressure in the gallbladder may be only 12 or 5 centimeters or even below zero. Cholangiography shows a flaccid gallbladder which does not evacuate its contents and a passive aspect of the common duct; the sphincter remains open (Fig. 7).

Idiopathic disease of the sphincter of Oddi (I) is recognized by cholangiography, as puncture of the gallbladder does not often give any definite manometric information. After injection of lipiodol, dilation and stasis of the common duct and its terminal stricture will appear (Fig. 8).

On the other hand, disease of the cystic duct can be distinguished by successively ascending curves, stabilizing at 30 centimeters of water and often higher. Since iodized oils cannot pass into the cystic duct, roentgenography would require the injection of a hydrosoluble contrast product into the gallbladder. However, recognition of their disturbing effects on biliary tonus led us to give up that method (Fig. 8). In fact, manometric findings constitute a basis on which to establish a diagnosis of disease of the cystic duct and to indicate a cholecystectomy. It is essential to know the functional status of the common duct. Usually the end of the cystic duct may be catheterized and then direct examination of the common duct may be performed under good conditions (Fig. 9).

In 1950, general statistics on 329 cases of idiopathic biliary dystonia and of dystonia associated with various anatomical lesions were presented. Those statistics corroborate the validity of the indications for peroperative manometric and roentgenographic examination in these cases when correlated with the operative results.

SUMMARY

A technique of peroperative manometric and roentgenographic examination of the biliary tract is presented. Between 1942 and September 22, 1951, 1,500 operations on patients have been performed, as well as extensive experiments on dogs.

The technique consists of two successive and independent steps: a manometric recording and a cholangiographic examination. The examination should be as simple, short, and standardized as possible.

Performed during a cholecystectomy, it demonstrates diverse pathological conditions which are factors in postoperative recurrences.

After removal of stones in the common duct it is possible to show that no other obstruction remains and to decide whether external drainage, primary suture, or a choledochoduodenostomy is required.

Manometric and roentgenographic examination for malignant obstructions of the common duct and for biliary functional disturbances by the method of puncture of the gallbladder are described.

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CHOLEDOCHOSTOMY WITH CHOLANGIOGRAPHY

A Review of 50 Cases

MEYER CORFF, M.D., SIMON BERGER, M.D., and J. GERSHON-COHEN, M.D.,
Philadelphia, Pennsylvania

IN 1949, Sterling and associates reviewed 50 cholangiograms done on 41 patients at this hospital, with the idea of clarifying the lack of precision in descriptions of the common bile duct.

This paper is an analysis, from a clinical point of view, of 50 cases of choledochostomy with 79 cholangiograms done on patients with biliary disease and possible common duct obstruction during the latter part of 1950 and the early part of 1951. Its purpose is to determine the efficiency with which we were treating these patients surgically, and the part played by cholangiography in these cases.

The desirability of doing choledochostomy along with cholecystectomy on the slightest suspicion of stone in the common duct is being preached in medical schools and clinics throughout the country. Yet it is not being done enough. Davidson and associates reported a series of 59 patients admitted for treatment of common duct stone. Of this group, in 29 per cent previous cholecystectomy had been performed and in 10 per cent cholecystostomy without common duct exploration had been carried out. In other words, 39 per cent of this group required reoperation because no common duct exploration had been done at the original surgery.

In the series of 50 cases we are reporting, 10 per cent required secondary surgery for the same reason.

At one time the added procedure of choledochostomy increased the operative mortality of cholecystectomy. In 1932, Lahey (14) reported that in his clinic simple cholecystectomy had a mortality of 4 per cent. This jumped to 13 per cent when choledochostomy was added. Cole, in a collective review of the mortality in cholecystectomy throughout the country in 1939, reported an over-all mortality of 6.5 per cent, which jumped to 10 per cent when choledochostomy was added. Today, however, the danger of the added procedure is practically nil. In this series we are reporting there was no mortality. In a series of 280 cases reported by Priestley, Walters, Gray, and Waugh of the Mayo Clinic (17) in 1949, where in addition to the removal of the gall bladder, an exploration of the common duct was made, there was not 1 death. A similar large series without a single mortality was reported by them (20) in 1948. The danger today is not in performing choledochostomy but in not doing it. When it is omitted and stone is retained in the common duct, a chain of events is started which may end in operation after operation, with all the attendant suffering, complications and, perhaps, mortality. This is especially true if complete obstruction of the biliary tree occurs, resulting in jaundice. Then the operative mortality increases. In a report from the Mayo Clinic in 1948, Waugh and associates (21) showed that the mortality of cholecystectomy in 78 jaundiced patients was six times that of 1,084 patients without jaundice. In the series reported by Gaster the hospital mortality was three times as high in the jaundiced patients as in the nonjaundiced patients. While no similar figures are available for patients jaundiced due to retained common duct stone, the mortality is certain to be many times higher than that of the nonjaundiced cases. Since jaundice is a common complication of retained stone, obviously everything possible must be done to reduce the number of such cases.

An analysis of a series of 50 cases in which the common duct was explored and in which 79 cholangiograms were done follows:

Mortality. There was no mortality in this series.

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Types of operation. In 80 per cent of the patients cholecystectomy and choledochostomy were carried out. In 10 per cent choledochostomy alone was done, as the gall bladder had been previously removed and the stone left in the common duct which had not been explored. This means that because the common duct was not investigated originally these patients were subjected to further major surgery with its accompanying danger. Six per cent had cholecystostomy and choledochostomy. This procedure was reserved for the aged and the very sick. Four per cent had cholecystojejunostomy and choledochostomy for inoperable carcinoma of the pancreas.

Reasons for exploration of common duct. In 40 per cent of the cases exploration was carried out because of the history or presence of jaundice. Thirty-four per cent were explored because of marked dilatation of the common duct. Twelve per cent were explored because the gall bladder was full of small stones which might easily have obtained access to the common duct. Four per cent were explored because stones were felt in the common duct on routine palpation. Two per cent were explored in an effort to find the cause of the patient's unexplained biliary symptoms. Two per cent were explored when x-ray examination done for something other than biliary disease showed stones in the common duct in instances in which the gall bladder had been previously removed. If we add chills and fever to the above list of reasons, then we have a textbook list of the indications for exploration of the common duct.

Percentage of stone found in common duct. The preoperative diagnosis of stone in the common duct is difficult and unreliable. McKittrick and Wilson reported that of 50 patients with one or more of the usual symptoms of common duct stone, stones were present in 80 per cent. On the other hand, 9 of 43 patients with no symptoms had stone.

In our series of 50 cases explored because of the possibility of stone in the common duct, stones were present in 48 per cent. This may be compared to a series at the Mayo Clinic, in which 52.8 per cent of common duct explorations revealed stone, and a series reported by Theissen in which 51.5 per cent showed stone.

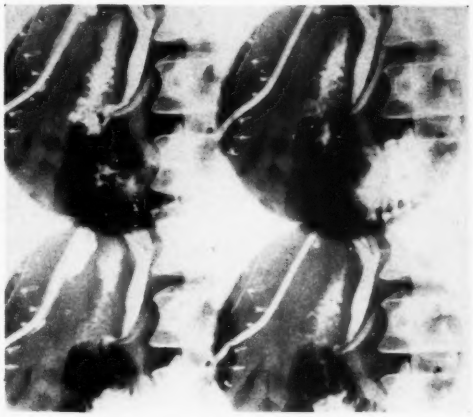

Fig. 1. Postoperative cholangiogram with normal biliary ducts. Also demonstrated is concomitant reflux of contrast material into the pancreatic duct.

Jaundice. In this series, 46 per cent of the patients were jaundiced or gave a history of jaundice. In all of these cases the common duct was explored. In 61 per cent the jaundice was due to stone. In 30 per cent the cause of the jaundice was not found. In all of these cases, however, the cholangiograms were normal before the patient left the hospital. It is assumed that in these cases the jaundice was due to an inflammatory lesion at or near the papilla of Vater, which caused a temporary obstruction. In 9 per cent of the cases the jaundice was due to the extrinsic pressure of a growth in the pancreas.

Stones in the common duct without jaundice. It is interesting to note that stones were found in the common duct in 41 per cent of patients without jaundice. This may be compared to Theissen's series in which 65 per cent of the patients had stones in the common duct without jaundice, and in McKittrick's series in which 20 per cent had stones and no jaundice. In other words, it is quite common to observe stones in the common duct, without jaundice. This, however, is no excuse for not exploring the common duct even though no symptoms are present. These stones may be innocuous when silent, but when they start to move toward the papilla they cause excessive pain, and when they obstruct the papilla they cause jaundice. There is no way of telling if and

Fig. 2. Cholangiogram on eighth postoperative day revealing two moderate sized stones in distal common duct with slight dilatation of duct.

when they will start to move. It is, therefore, imperative that they be removed.

Cholangiograms. In all, 79 cholangiograms were done on 50 patients. Cholangiograms of 17 of these patients were made in the operating room, 2 cholangiograms in the case of 1 patient. Of the 18 operating room cholangiograms, only 2 were of the immediate type, being done through the cystic duct stump. The remainder were done through a T-tube after exploration had been carried out. Of the operating room cholangiograms 10 showed a normal tract in which the diodrast flowed normally into the duodenum. Four showed stones in the common duct. Three showed obstruction due to extrinsic causes, and 1 showed a polyp in the common duct. From the 61 cholangiograms done through T-tubes in from 5 to 18 days after operation, 32 patients were shown to have a normal tract. Multiple cholangiograms were made in the remainder. In 9 patients stone was shown to be retained in the common duct and in the balance some type of extrinsic pressure, such as carcinoma of the pancreas, localized adhesions, and pancreatitis, caused the obstruction.

Retained stone in the common duct. Stone retained in the common duct after surgery and shown by postoperative cholangiogram is unfortunately too common throughout the country. In Hughes' series of 46 patients, 24 per cent had retained stone and underwent further surgery. In Theissen's series of 33 patients, in whom postoperative cholangiograms had been done, 15 per cent showed retained stone. Our series of cases showed 18 per cent. Hicken's (11) series of 100 cholangiograms showed 12 per cent retained stone. One of the best reports is that of McKittrick which showed only 2 per cent retained stones.

In our series, of the 9 patients (18 per cent) whose postoperative cholangiograms indicated stone in the common duct 7 were treated by the Pribram ether method. Of these, treatment was successful in 4. Three patients returned within 1 year for reoperation. In the remaining 2 cases, the T-tubes were accidentally removed about 2 weeks after operation. In spite of stones still being present, in both cases the sinuses healed within 72 hours and the patients were discharged shortly thereafter. In these cases the obstruction must have been incomplete, since the patients were not jaundiced and did well after discharge. This phenomenon of healing sinuses with stones in the common duct happens often according to Hicken (11). He showed recently that in 35 patients proved by cholangiogram to have residual stones in the common duct, a persistent sinus did not develop in any instance when the T-tube was removed. In 32 cases the tract closed over in 72 hours. In 3 cases drainage continued from 1 to 4 weeks before healing. Healing failed to occur only in those cases in which the stones caused a complete obstruction of the distal segment. These patients came to secondary surgery.

DISCUSSION

What are some of the reasons stones are left in the common duct?

Hepatic stones. It is felt that some of these retained stones may originate in the hepatic radicles. In irrigating the common duct and the hepatic ducts at operation, they may be loosened but it is possible that they may not descend until perhaps a week later, when the postoperative cholangiogram shows them lodged in the common duct. In numerous cases by use of the lithophone, we have located a stone in one of the hepatic radicles which we

ha missed by use of the scoop and irrigation. Li ewise, stones have been brought down fr n the hepatic ducts by irrigation which w done in spite of the belief that there were n more stones in the biliary tract. It is be- li ed that this type of stone which descends fr n the hepatic radicles a few days post- o ratively makes up a fair percentage of the r ained stones.

nomalies. In our own series, anomalies p yed no role in the retention of stones in the c mmon duct. As a matter of fact the only a maly in the series was a case in which the g l bladder was congenitally absent and the st nes were in the common duct and were c mpletely removed, as shown by a post- o rative cholangiogram. However, Collet and associates reported 4 anomalies which were the definite cause of retained stones. In 1 case, what was thought to be a common duct full of stones proved to be the right hepatic duct. This was emptied of stones but the multiple retained stones were those in the real common duct. The retained stones and the anomaly were found only because a post-operative cholangiogram was done a few days after the original surgery.

Anatomic difficulties. Whatever the anatomic difficulties are, they are a source of retained stone in that they do not allow adequate examination of the common duct. When the patient is too obese the duct is often deep and hidden by fat and must be dug out. When the surgeon must work deep under the costal margin, again exploration of the common duct is difficult and is usually incomplete.

When the gall bladder, the cystic duct, and common duct are thickened and edematous from acute inflammation, once more, thorough exploration of the common duct is difficult and stone may be left in.

Acutely ill patients. Occasionally incomplete exploration is done because the patient is not in good condition on the table. It is usually in the very aged or the very sick patient in whom perhaps a cholecystostomy is anticipated that the common duct is hurriedly explored. When this is done there is always a good chance that stones may be left in.

What can be done to lower the incidence of stone left in the common duct?

Fig. 3. Cholangiogram on twenty-third postoperative day. Since previous study, ether-alcohol flushing through T-tube performed. Previous stones are no longer visualized. Caliber of duct is normal.

Use of the left side of the table. One of the means of reducing the number of stones missed by palpation is to do that palpation from the left side of the table with the left hand. The great percentage of surgeons, by far, operate on gall bladder patients and palpate the common duct from the right side. Often this is very difficult. Especially is this true in the obese or the poorly relaxed patient. In these same cases palpation of the duct is much easier if done from the left side of the table with the left hand. The index or middle finger can be placed in the foramen of Winslow and the common duct rolled between it and the thumb. In this position the hand is in a naturally flexed and relaxed position. There is no strain upon it and the examination is more accurate. It is not the answer to the retained stone problem since palpation alone, in the best hands, is still unreliable. However, it does afford some help. Gerwig, Jr., in a recent editorial, advised not only palpation from the left side of the table but operation also. He believes that because of the anatomical position of the gall bladder and common duct it is easier to deal with them from the left. McKittrick and Wilson advocate a similar policy, stating that the common duct is felt most easily from the left side of the table, especially if it is felt over a probe or dilator placed in it.

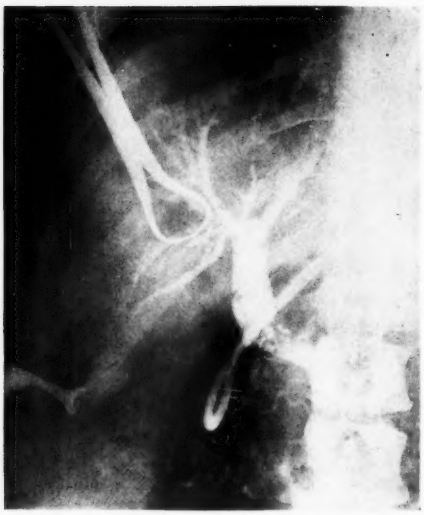

Fig. 4. Operative cholangiogram. Dye injected through T-tube. The lack of any contrast material entering duodenum and dilatation of ducts indicated obstruction at ampulla of Vater. The tortuous linear opacity is a radiopaque impregnated sponge.

Use of the lithophone. It is well known that the best surgeons can miss a stone in the common duct when palpation alone is depended on. Even if irrigation and probing of the duct are added, still a fair percentage of stones are missed. Any device then which will reduce the fallibility of the surgeon is welcome. Such a device is the lithophone, which electrically magnifies the sound made when a stone is struck by a metal probe to which the instrument is attached. It is especially good in the detection of stones far up in the hepatic ducts, since these stones are not at all palpable. Although not infallible, the lithophone has often picked up stone in the duct which has been missed by palpation, irrigation, and scooping.

Use of cholangiograms at the operating table. Hicken (11) classifies cholangiograms at operation into the following types:

The scout cholangiogram, in which the gall bladder is aspirated of all its bile and 40 to 50 cubic centimeters of diodrast are injected. This contrast material fills out the gall bladder, cystic and common ducts, and the hepatic radicles.

The choledochogram, in which the diodrast is injected via the common duct. In this type the cystic duct is either clamped or divided.

Utilization of the cystic duct stump.

Ampullary (retrograde) injection. This is done in certain cases in which the duodenum has been opened and stones removed from the lower end of the common duct by dividing the ampulla. The condition of the rest of the biliary tract can be determined by injecting diodrast into the opened ampulla in a retrograde manner.

The completion cholangiogram, done by injecting the diodrast through a T-tube in the common duct at the end of the operation.

The first three types may be classified as immediate cholangiograms, in that they are done *before* the common duct is opened. The last two may be called completion cholangiograms, since they are done *after* the common duct has been opened.

When the gall bladder is to be removed because of stones, the cholangiogram that seems most logical to us is one of the immediate types, in which the diodrast is injected through the cystic stump before the common duct is opened. The picture can be taken, and while it is being developed the gall bladder can be removed, thus saving time in the operating room. The film may show that there are no stones in the biliary tract and that the diodrast runs through into the duodenum without difficulty. In such a case the cystic stump is ligated and there will be no need to open the common duct. If, on the other hand, the cholangiogram shows, say, 6 stones, then the common duct is opened and the exploration is continued until the 6 stones are removed. Knowing ahead of time the number of stones present obviates any being left, and the patient will be saved possible surgery in the future. Hagan and Townsend advocate this type of cholangiogram to be used routinely in all elective cases of chronic cholecystitis and cholelithiasis. In our own series, only 11 per cent of the operating room cholangiograms were of the immediate type. These showed normal biliary tracts. It will be recommended that more of the immediate type be done and also that more operating room cholangiograms, as a whole, be done.

n a short while a new set of operating ro ms will be opened at this hospital. The ra iology department has promised the surge n two more aids in decreasing the incidence of etained stone. One of these aids is special flu roscopic equipment which may be used to de ect stones in the biliary system. This will de ect stones which are fairly large and in fa ly thin people. It is agreed, however, that in very obese patients, and in patients with sm ll nonobstructing stones, this equipment is not of very much value. In such latter ca es, the use of the second aid, namely the pe aroid cassette, is indicated. This was re ce tly introduced and is not as yet readily av ilable. However, reports of it offer great pr mise for quicker and more accurate operative cholangiography.

Fig. 5. Postoperative cholangiogram through cholecystostomy tube revealing the gall bladder, cystic and common ducts to be packed with faceted calculi.

COMMENT

One of the most frequent operative problems after cholecystectomy for stones is the problem of retained stone in the common duct. No surgeon and no clinic have escaped this problem. It is the result of either failure to explore the common duct, or of incompletely exploring it. In a certain percentage of cases, it may result from stones moving down from the hepatic radicles after exploration.

The most prevalent method of exploring the common duct is incision, use of the stone forceps to catch and remove stones, and finally, vigorous saline irrigations. In an effort to prove that the common duct is then emptied, a probe is placed into the duct and passed down through the papilla of Vater into the duodenum, or saline is injected through a T-tube. If either the probe or saline enters the duodenum, the duct is said to be free of stones. This time-honored method is definitely unreliable as shown by the high percentage of retained stones reported by many clinics. Time after time the surgeon has felt the common duct to be empty after all the procedures mentioned have been carried out, only to find that the postoperative completion film reveals stone.

In the interest of reducing the figures on retained stone, the following suggestions are made: (1) routine exploration of the common duct on the suspicion of stone; (2) more accurate palpation of the common duct by palpation from the left side of the table; (3) more frequent use of the lithophone; (4) the routine use of immediate cholangiogram in the operating room whenever there is the slightest indication; (5) routine use of completion cholangiogram for check-up after choledochostomy.

SUMMARY

The cases of 50 patients who had choledochostomies and 1 or more cholangiograms done are reviewed.

1. There was no mortality in this group.
2. The types of operation in addition to the choledochostomy are given, 80 per cent being cholecystectomy.
3. The indications for the common duct exploration are given, the most frequent being jaundice or a history of jaundice.
4. There is a breakdown given of the causes of the jaundice, the greatest number (61 per cent) of which were due to stones in the common duct.
5. The types and numbers of the cholangiograms are given with a discussion of the most logical one (through the cystic duct stump).

6. Retained stone in the common duct (18 per cent) is discussed.

7. Suggestions for the prevention of retained stone are made.

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FURTHER EXPERIENCES WITH LOCAL AND SYSTEMIC BACITRACIN IN THE TREATMENT OF VARIOUS SURGICAL AND NEUROSURGICAL INFECTIONS AND CERTAIN RELATED MEDICAL INFECTIONS

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THE antibiotic bacitracin was discovered by one of us (B.A.J.) in the Laboratory for Bacteriological Research of the Department of Surgery of the College of Physicians and Surgeons, Columbia University, in June of 1943 (15). It is produced by a gram-positive aerobic spore-forming bacillus, at first classified as a member of the Bacillus subtilis group, but more recently placed in the category of Bacillus licheniformis by Dr. Kenneth Burdon of Baylor University and by Dr. Nathan Smith of the Food and Drug Administration.

The antibiotic was first produced in plain broth media and it was demonstrated that the filtrate could be injected into the center of an infectious lesion and within a short period of time bring the infection under control, or it could be applied to the surface of an infected wound or ulcer with the same result. The antibiotic was partially purified and concentrated first in the chemical laboratories of the Department of Biochemistry of the College of Physicians and Surgeons by Dr. Herbert Anker and was later produced commercially, and made available for clinical use. The first patient was treated on October 11, 1943, with the crude filtrate of the culture, for a furuncle inside the right nostril. The infection promptly resolved. The first 100 cases treated locally with this antibiotic were reported in the March number of the *Journal of the American Medical Association* in 1947, with a favorable response in 88 per cent of the cases (25).

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The first 6 were treated with the crude filtrate, the next 30 with the concentrated preparation from the chemistry laboratory, and the last 64 with the commercial product.

During this time efforts were being made to purify the antibiotic further, in order to have it available for systemic administration. The first material considered to be sufficiently pure for systemic use was produced during the summer of 1946. After a period of observations on animals and a series of injections into ourselves and other members of the laboratory staff, the first patient was treated systemically on October 11, 1946, for an "undermining burrowing ulcer" of the axilla. With the aid of this new antibiotic applied locally and given systemically after excision of the ulcer, a primary skin graft was successful. Formerly this was impossible in similar cases.

The first commercial product was made by the surface growth of the organism on agar medium in bottles, in a manner similar to the early production of penicillin. But later a way was found of producing bacitracin in deep tanks in large quantities. Although it was found that the systemic administration of bacitracin made by the surface growth method caused a transient albuminuria, this was considered to be of no clinical significance. Soon doses were being increased from 10,000 units every 6 hours up to 50,000 units, for a total of 200,000 units a day. A tentative toxicity specification thought to be safe, namely, an LD_{50} of 200 units for a 20 gram mouse, was set up in January, 1948, by the Food and Drug Administration based upon this experience. When the deep tank product became available, these same large doses were given by several different observers, who had been

TABLE I.—INCREASE IN RESISTANCE TO PENICILLIN OF COAGULASE-POSITIVE STAPHYLOCOCCUS AUREUS*

Year	No. of strains	Per cent resistant
1947–1948	286	17.8
1949	228	29.1
1950–1951†	269	43.47
1951‡	293	43.0

Method: Blood agar plate, filter paper disc.
*Cultured from surgical infections treated in the Out-Patient Department of the Presbyterian Hospital, New York.
†Late 1950 through January, 1951.
‡July, August, September, 1951.

selected to appraise the efficacy of the new antibiotic. It was soon found that in certain individuals, this new preparation produced symptoms of lower nephron nephrosis. At the same time, it was demonstrated that these large doses delayed tubular and glomerular filtration (29). A few cases showed a temporary suppression of urine and a disturbing rise in the nonprotein nitrogen. Furthermore, albumin appeared in considerable quantities in the urine with granular casts, epithelial cells and white cells, and occasionally red cells. Although these evidences of nephrotoxicity were reversible and no fatalities could be attributed to it, the report was rapidly spread abroad that this new antibiotic was not safe to use (40). It was decided to discontinue systemic treatment until the cause for the nephrotoxicity could be found.

A careful study of these cases demonstrated that the deep tank method had resulted in a product which was definitely more toxic than the surface growth material. It was also found that different deep tank lots varied markedly in toxicity, some being more than twice as toxic as others. When the less toxic lots were used in doses limited to 80,000 to 100,000 units a day, the evidences of kidney irritation were inconsequential and always reversible, and these doses were in most cases clinically effective.

In December, 1949, a series of 270 cases of infections was reported treated systemically with bacitracin (26). The first 85 cases received the surface growth product, the next 85 the early and relatively toxic product made by the deep tank method, and the last 100 were treated with material which exceeded the tentative Food and Drug Administration specification mentioned. With this material the LD50 proved to be 500 units for a 20 gram mouse. A corresponding dose for a 50 kilogram man would be 1,250,000 units. We now believe this to be the minimum requirement for safety and we have requested the Food and Drug Administration to make this specification official. This should give a wide margin of safety, if the dose for an adult is kept below 100,000 units a day given intramuscularly in divided doses. Half of this dose is usually sufficient for a therapeutic effect with infections due to susceptible organisms.

Bacitracin is not absorbed to any degree from the intestinal tract. When given by mouth it materially reduces the number of susceptible organisms in the alimentary canal, including the clostridia, the gram-positive cocci and amebae. Although it may be given slowly and continuously by vein or artery, if these routes are particularly indicated, the intramuscular route is by far the most convenient and safest way to administer bacitracin systemically.

THE LOCAL ADMINISTRATION OF BACITRACIN

Since the report of the first 100 cases of surgical infections treated locally with bacitracin, countless numbers of localized infections have been so treated either with aqueous solutions or with ointments, and many authors have attested to its efficacy.

Surgical infections. In the last 4 years there has been demonstrated a steadily increasing resistance of Staphylococcus aureus to penicillin, as is shown in Table I, which gives figures for cultures derived from infections seen in the Surgical Out-Patient Department of the Presbyterian Hospital in New York City. This confirms results reported by Barber from England and by Pulaski in this country (39). Our figures suggest that this trend may have come to a standstill, but as the cases come to us, only about half can be expected to respond to penicillin.

Since July, 1950, all cultures in the Surgical Bacteriology Laboratory of the Presbyterian Hospital have been routinely tested for susceptibility to penicillin, bacitracin, streptomycin, and terramycin. The combined re-

sults of two specified periods during this time appear in Table II and indicate that many other organisms beside staphylococci were resistant to penicillin and that of all the antibiotics, bacitracin has the highest potency in all of the bacterial categories of gram-positive organisms. When these organisms are present, it would seem to be the drug of choice. If gram-negative rods are also present as secondary contaminants and if they are susceptible, it is reasonable to combine bacitracin with streptomycin, terramycin, or possibly neomycin. Bacitracin may be the treatment of choice for these local infections, because it not only has a wide antibacterial spectrum, but it is not inhibited by the penicillinase-producing contaminants and it has a very low incidence of allergenicity.

Several authors have confirmed our early results (25) with successful local treatment in surgical infections (1, 3, 12, 18).

Bacitracin remains stable in lyophilized form in sterile bottles at room temperature for a year or more. It may be dissolved in saline or water so as to give solutions of 500 units or 1,000 units per cubic centimeter. It is convenient to combine equal parts of 2 per cent novocain with a bacitracin solution containing 1,000 units per cubic centimeter. Such a mixture may be injected with a sharp or blunt hypodermic needle directly into the center of a furuncle, which will often be quickly aborted by the introduction of 0.1 cubic centimeter. Larger furuncles may require 0.2 or 0.3 cubic centimeter and carbuncles 0.5 or even 1 cubic centimeter. With carbuncles, if there is a small central area of necrosis and a wide zone of induration, bacitracin and novocain solution may be injected in small quantities, not over 1 cubic centimeter, in a circumferential manner in 6 to 8 places close to the margin of induration. The novocain minimizes the pain and although the first injection may be moderately painful, this distressing symptom passes off after a few minutes and subsequent injections of the same kind on succeeding days are usually not painful. If there is a well localized abscess either beneath the skin or in the deeper tissues, instead of making an incision for drainage, a cure may often be effected by aspirating the contents of the abscess cavity as completely as possible and introducing 2 to 5 cubic centimeters of bacitracin containing 1,000 units per cubic centimeter. If there is any reaccumulation of the exudate, it may be reaspirated and bacitracin again injected on subsequent days. In many cases the infectious process resolves after 2 or 3 aspirations and injections and a surgical procedure is obviated.

As much as 5 or 10 cubic centimeters may be injected into such cavities, depending upon the size, and there is no fear of nephrotoxicity from doses up to 50,000 units a day. This would be contained in 100 cubic centimeters of solution, and for most large abscess cavities 10 cubic centimeters would be sufficient. The larger amounts may be introduced into the pleural cavity, the pericardium, the peritoneum, or into joint cavities in a concentration of 500 to 1,000 units per cubic centimeter without any evidence of local irritation. Bacitracin may also be introduced into an abscess cavity by attaching a No. 20 intramuscular needle to a small portion of plastic tubing, which may be placed exactly where needed. This permits the instillation of bacitracin every 2 or 3 hours. Bacitracin may be delivered in this way to infected wounds. If necrotic tissue has to be removed, as in cases of chronic osteomyelitis, as soon as the dead bone has been removed, the resulting wound

TABLE II.—PERCENTAGE OF SENSITIVITIES TO THE FOUR ANTIBIOTICS AVAILABLE FOR LOCAL APPLICATION, JULY TO DECEMBER, 1950 AND JULY TO OCTOBER, 1951*

Organisms	No. of strains	Per cent sensitive to:			
		Penicillin	Bacitracin	Streptomycin	Terramycin
Staphylococcus aureus†	449	55.9	97.3	93.6	95.5
Beta hemolytic streptococcus‡	60	90.0	100.0	48.3	95.0
Nonhemolytic streptococcus	43	51.1	93.0	25.5	86.0
Coliforms	43	—	—	88.3	95.3
Proteus	22	—	—	68.1	18.1
Pyocyaneus	17	—	—	41.1	35.3

*Organisms cultured from 492 infections treated in the Surgical and Dermatological Clinics of the Presbyterian Hospital, New York.
†Coagulase-positive.
‡Not grouped.

should be flushed with bacitracin solution containing 1,000 units per cubic centimeter. A silk tampon should be inserted into the cavity and this packed with coarse meshed gauze wet with the antibiotic solution. The packing may then be changed daily leaving the silk tampon intact until the wound surface has been completely covered with granulation tissue, at which time it may be closed secondarily, or covered with skin grafts.

Bacitracin may also be applied to infected burns, ulcers or wound surfaces in ointment form. The best vehicle that we have found is a carbowax base made up of two parts of carbowax 4,000, five parts of carbowax 1,540, and five parts of polyethylene glycol (carbowax 300). These proportions may need to be changed slightly in order to give the ointment a soft consistency at different seasons of the year. The carbowaxes are put together and sterilized in a water bath or in a dry oven. When the mixture cools, the antibiotic may be added in a concentrated form so as to yield 500 units per gram of ointment. Bacitracin is readily liberated from this vehicle and is absorbed to some extent from the surface of the wound. Very low levels of the antibiotic are found in the blood stream and somewhat higher levels in the urine, but there is never any evidence of nephrotoxicity. Manufacturing concerns have put out bacitracin in a petrolatum base, in which it is more stable and therefore more suitable for storage and transportation, but when bacitracin ointment can be made up in a pharmacy fresh from day to day or week to week, the carbowax base is preferable.

Cases which illustrate the local use of bacitracin in surgical infections may be briefly summarized as follows:

L. B. This man complained of a painful swelling beneath the chin of a week's duration with difficulty in swallowing. There was an abscess about 4 centimeters in diameter, standing out from the surface about 2.5 centimeters. The center was covered by a small scab. On removing the scab, a tiny droplet of pus came out, from which a culture was taken. With a blunt needle 2 cubic centimeters of bacitracin containing 2,000 units were injected and on withdrawing the needle a large quantity of pus and some slough drained out. Another 0.5 cubic centimeter of bacitracin was then instilled and a dry dressing was applied. The culture showed a hemolytic Staphylococcus aureus, coagulase-positive, and sensitive to both penicillin and bacitracin. Twenty-four hours later the lesion was almost flat and there was no longer any difficulty in swallowing. Bacitracin was again instilled and part of this drained out mixed with pus. Another 0.5 cubic centimeter of bacitracin was injected. On the following day discharge had practically ceased. When seen 6 days later, the area of the abscess was entirely flat and the wound well healed.

This case illustrates the cure of an abscess by aspiration and instillation with bacitracin, obviating the necessity for surgical drainage.

A. B. This elderly lady entered the hospital complaining of two extensive ulcers on the right leg. The larger one on the outer side measured about 12 by 5 centimeters and was of 18 months' duration. The smaller one, on the inner side, was of 6 months' duration. The lesion had started as a small scratch on the outer surface. Infection set in and spread "like wildfire," forming a large ulcer. Her local doctor excised the area of ulceration and applied zinc peroxide. The wound became clean and a skin graft was attempted. This seemed to take well at first, but in about 10 days the infection flared up again. The lesion was again excised, but this did not bring the infection under control. After 1 year a similar lesion developed on the inner surface of the leg and both extremely painful ulcerations persisted up to the time of admission. There was profuse exudate on the surface of pale granulations and considerable swelling of the whole area, but there was no gangrene of the skin and no extensive undermining. The cultures revealed a coagulase-positive hemolytic Staphylococcus aureus and a nonhemolytic streptococcus, both resistant to penicillin and susceptible to bacitracin. Bacitracin in a carbowax base was applied to the ulcerated areas and the patient had a good night's sleep for the first time in weeks. The infection subsided rapidly. Bright red granulations grew up and new skin began to grow in from the margins. On the ninth day both areas were covered by small deep Davis grafts taken from the thigh. These were held in place with a single layer of coarse meshed gauze covered over with a thick layer of cotton wet with saline and sealed with a double layer of zinc oxide ointment gauze. All of the grafts took satisfactorily and soon fused together covering over both areas with vigorously growing epithelium.

This case illustrates the rapid control by bacitracin ointment of a longstanding, exceedingly painful, incapacitating, double, infectious ulceration of the leg, permitting a successful skin graft.

W. W. This patient had a carbuncle of the lower lip of 3 days' duration, involving about half of the lip somewhat more on the left than on the right of the

midline. There was an area of slough near the right extremity and two smaller openings on the left with undermining of the mucous membrane. He had been given 300,000 units of crysticillin for 2 days without any effect on the lesion. Therefore a culture was taken and bacitracin solution containing 1,000 units per cubic centimeter was instilled into the center of the lesion through the openings with a blunt needle and bacitracin ointment was applied. The culture yielded a coagulase-positive hemolytic Staphylococcus aureus, susceptible to both penicillin and bacitracin. The following day the lesion was very much improved with less induration and discharge. A small amount of slough was removed and bacitracin solution was again instilled. On the following day the process had almost completely subsided. The openings had dried up and were sealed with scabs. It was impossible and unnecessary to give any further injections. Healing progressed rapidly.

This case illustrates a dangerous carbuncle of the lower lip responding promptly to the local injection of bacitracin solution after systemic penicillin had failed.

E. R. This patient had had a sebaceous cyst in front of the lobe of the right ear for 2 years. Two days previous to examination it had become red, swollen, and painful, obviously infected. Novocain and bacitracin were injected and reaspirated mixed with pus. On the following day the inflammation had subsided considerably and another 0.5 cubic centimeter of bacitracin was injected and part of it reaspirated. Two days later, inflammation had entirely disappeared and 5 days after that, under novocain anesthesia which contained bacitracin, the area of the cyst was removed and the wound was closed primarily with silk sutures. The wound healed by primary union. No culture was taken, because the pus was mixed with bacitracin, but the rapid response to bacitracin treatment indicated that the organism was susceptible.

This case illustrates the prompt subsidence of inflammation in an infected sebaceous cyst following the injection of bacitracin, permitting, 1 week later, an excision and successful primary closure.

Neurosurgical infections. In neurosurgical infections the local instillation of 5 to 10 cubic centimeters of a bacitracin solution containing 500 to 1,000 units per cubic centimeter intrathecally by lumbar or cisternal puncture, into the ventricle, or into the cavity left after excision of a brain abscess, is well tolerated once or twice a day without any signs of toxicity. This local use is probably more important than the intramuscular injections in such cases because of the difficulty bacitracin has of passing the blood-brain barrier. Details of local treatment in neurosurgical infections have been given in other reports (44, 45, 46).

Skin infections. There have been numerous favorable reports in the dermatological literature regarding the local use of bacitracin in the pyodermas (5, 8, 9, 10, 28, 30, 31, 48).

Eye, ear, nose and throat infections, respiratory infections, and intestinal infections. Inasmuch as bacitracin is not readily absorbed from the digestive tract (20, 42), administration by mouth may be considered local treatment for infections of the mucous membrane lining of the alimentary tract and the respiratory tract. Even with oral doses of 250,000 units a day, blood levels are hardly detectable, although bacitracin may be found in the urine in a concentration of 1 to 2 units per cubic centimeter. From 25 to 30 per cent of the amount given by mouth may be recovered from the stool. This means that it is available for its antibacterial action against susceptible organisms. The anaerobic streptococci and spirochetes of the mouth are particularly susceptible as are the aerobic hemolytic streptococci which commonly cause acute tonsillitis and pharyngitis. The enterococci and clostridia of the intestine also yield to its action.

Bacitracin in tablet or troche form containing 1,000 units per tablet is effective in acute inflammation with or without ulceration in the oral cavity. So far as the authors have seen, there has been no evidence of local irritation or allergic response, which is so common when penicillin is given by mouth (7).

Bacitracin in ointment form has been especially prepared for conjunctival infections and it has proved effective in cases due to streptococci, staphylococci, and pneumococci. It may be used as a prophylactic against gonococcal infections in the newborn (4). The local application of saline or aqueous solutions containing 500 to 1,000 units per cubic centimeter to inflamed mucous membrane of the conjunctivae and paranasal sinuses is also often rapidly effective in eliminating susceptible organisms and resolving the infectious process. It is essential that such solutions should come in close contact with every part

of the infected surface. This is often difficult in sinus infections, even with the Proetz method (35, 43). Ophthalmologists and otolaryngologists have been particularly impressed with the low incidence of allergic reactions which are so commonly seen following treatment with penicillin.

Bacitracin has been used locally also as an aerosol for lung infections, particularly in conditions such as bronchiectasis. It has been used both alone and combined with penicillin, when synergism has been demonstrated by the antibiotics against the infecting organisms (36, 37, 38).

Favorable results have also been observed in cases of regional enteritis, in ulcerative colitis, and particularly in cases of amebic dysentery. In intestinal infections 6 to 8 tablets a day should be given, each tablet containing 10,000 units. Improvement in the first two diseases mentioned is gradual and not dramatic and it may not be successful in more than half of the cases, but in amebic colitis the symptoms disappear promptly and there is usually rapid healing of the ulcerations as seen by proctoscopy. In the great majority of cases the amebae disappear from the stool and a cure results. About 25 per cent may have a late reappearance of the organisms in the stool without clinical symptoms. A second or third series of treatments may be necessary to eradicate them completely (6, 14, 17, 32, 33, 34).

In intestinal infections and for reducing the intestinal flora before surgical procedures on the intestine, combinations of bacitracin with antibiotics effective against the gram-negative aerobic rods are clearly indicated. Just which combination is most effective in these conditions requires extensive clinical and laboratory study. The occurrence of moniliasis after treatment with some of these other antibiotics must be kept in mind. This has not been observed after bacitracin, as far as we know.

THE SYSTEMIC ADMINISTRATION OF BACITRACIN

Since the preliminary report on the first 105 cases treated by the systemic administration of bacitracin in 1948 (24), experience has been limited because of the occurrence of disturbing nephrotoxicity when the first material produced by the deep-tank method was employed. This began with the last few cases of that preliminary series and the explanation could only be found by a careful analysis of the early cases treated with the deep-tank material. When it was discovered that disturbing nephrotoxicity could be avoided by employing lots which met the specification of LD_{50} of 500 units for 20 gram mice and by limiting the dosage to 100,000 units a day, confidence in the efficacy and safety of systemic bacitracin was restored, as described in the second publication (26). Since then others have confirmed these results, among them, Longacre and Waters (19), Reisner, Bailey and Appelbaum, Volini and Kadison (47), Friedberg and Bader, and Grabscheid.

The present authors, after a careful analysis of the last 160 cases which they have treated, are willing to recommend the wider employment of material now available by any doctor who can follow his case with the necessary laboratory studies and with the following limitations of dosage in mind. It is believed that with continued efforts at purification by the three manufacturers now producing bacitracin, the specifications for toxicity may be further raised and the margin of safety further increased.

Method of management. Bacitracin is much more slowly eliminated through the kidneys than is penicillin, measurable amounts being present in the blood for 6 to 8 hours after injection. In the previous reports (24, 26) the majority of the patients received an intramuscular dose every 6 hours. It has recently been found that injection every 8 hours is clinically effective and is much more convenient for the patient and for the nursing staff. Dosage may be estimated roughly from 200 to 400 units per kilogram of body weight. The upper limit of this dosage would give a 50 kilogram man 20,000 units and a 70 kilogram man 28,000 to 30,000 units for a total of 60,000 to 90,000 units a day. Only under unusual conditions should the dosage be more than 100,000 units a day in divided doses, for reasons discussed later.

The material should be dissolved in the appropriate amount of 2 per cent novocain

in saline, so as to reach a concentration of 10,000 units per cubic centimeter. This should be injected into the muscles of 4 or 6 different areas in rotation, in order to minimize the local pain which varies considerably in different individuals. Occasionally a patient with a low threshold for pain is considerably disturbed by these injections, particularly if they are given twice in the same area, while others take them without difficulty. If given intravenously or intra-arterially, bacitracin should be administered slowly in a saline infusion and not more than 10,000 units given over a period of 4 hours.

Some patients complain of loss of appetite, others of nausea, and a few patients vomit. These symptoms may be considerably reduced by administering dramamine and they are not an indication for stopping treatment unless the vomiting is so frequent that it interferes with nutrition. The urine should be kept alkaline with the oral administration of sodium lactate or sodium bicarbonate with each injection of bacitracin. The fluid intake and output should be carefully measured each day. At first there is often an increased urinary output. If there is a decrease, it should be carefully watched and treatment stopped, if the output gets down to 500 cubic centimeters a day for adults or corresponding quantities for children. The blood urea nitrogen should be measured before the administration of bacitracin and twice a week thereafter, until a week or 10 days after treatment has been discontinued. There may be a slight rise in blood urea nitrogen during the course of treatment, but unless the initial figure is doubled, there is no indication for stopping treatment. The urine should be examined daily for albumin, casts, and cellular elements. These may be expected to appear on the third or fourth day, but usually with continued treatment they disappear again or are considerably reduced, indicating that the kidney in some way adapts itself to the drug during the course of treatment. After it is stopped, all of these abnormalities disappear. Every patient who has had any evidences of nephrotoxicity and who has not died of his infection per se, has come back for re-examination and it has been found that the albumin has disappeared from the urine and the blood urea nitrogen, if it had risen, has returned to normal.

Treatment should be continued in systemic cases generally for a week or 10 days. Whenever necessary, however, it may be carried on longer. One patient in this series with Behcet's syndrome (Series No. 1085) was given 20,000 units intramuscularly twice or three times a day over a period of 10 months, with a total of more than 10 million units, without any evidence of residual kidney irritation. Another patient (Series No. 1072), reported previously (26), took 10,000 units every 8 hours for 50 days and 20,000 units every 8 hours for 83 additional days with only occasional albumin in the urine and no change in the nonprotein nitrogen.

Method of appraisal. The following portion of this report presents an analysis of the last 160 cases treated with intramuscular injections of bacitracin. These represent all of the cases treated under the direction of the authors since the publication in December of 1949 of the first 270 cases (26) up to the time of the preparation of this paper. Many of these cases were referred to the authors when all other treatment had failed and when all hope was gone. A number of the cases were moribund when bacitracin treatment was started. When called for in desperate cases, bacitracin was never refused. Some of the referred cases were transferred to the Presbyterian Hospital in New York, but many were treated in nearby and suburban hospitals.

These 160 cases may be divided into five groups (Table IIIa), the largest containing 85 various established surgical infections which were treated either directly or indirectly by the senior author (F.L.M.). A small group of 8 of his surgical cases form the second group. These received bacitracin prophylactically at the time of operation because infection was anticipated. The third group comprises 24 medical infections related in one way or another to the practice of surgery. Their treatment also was directed by the senior author. Most of the cases in the fourth and fifth groups were treated directly or indirectly by the junior author (P.T.). There were 22 established neurosurgical infections which received intrathecal, intraventricular, or intra-

TABLE IIIa.—OVER-ALL RESULTS OF BACITRACIN THERAPY IN 160 CASES

	Total No. cases	Results of treatment							
		Excellent		Good		Questionable		No effect	
		No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Surgical infections	85	23	27	41	48	18	21	3	4
Prophylactic surgical cases	8	0	—	7	88	0	—	1	12
Related medical infections	24	13	54	8	33	1	4	2	8
Neurosurgical infections	22	5	23	14	64	1	4	2	9
Prophylactic neurosurgical cases	21	0	—	13	62	6	29	2	9
Totals	160	41	26	83	52	26	16	10	6

Excellent and good (favorable) results in 78 per cent of cases
Questionable and no effect (unfavorable) results in 22 per cent of cases

TABLE IIIb.—RESULTS IN 43 CASES RECEIVING SYSTEMIC BACITRACIN ONLY AND IN 117 RECEIVING BOTH LOCAL AND SYSTEMIC THERAPY

Treatment	Total No. cases	Results of treatment				
		Excellent No.	Good No.	Per cent favorable	Questionable No.	No effect No.
Systemic only	43	18	13	72	7	5
Systemic and local	117	23	70	79	19	5
Totals	160	41	83	78	26	10

cerebral bacitracin and intramuscular injections as well. It was also used prophylactically in 21 neurosurgical cases in which the development of infection was to be anticipated.

The clinical and laboratory data from these 160 cases have been analyzed from many standpoints, the most important of which are: the clinical diagnosis, the duration of illness before the administration of bacitracin, the previous treatment, the bacteriological findings, the results of tests for the sensitivity of the organisms either causing the infection or present as secondary contaminants, the dosage of bacitracin, the intervals of administration, the duration of treatment, the evidences of toxicity, the synergistic action of bacitracin with other antibiotics, and the accompanying surgical procedure, if any. All of these factors have been correlated with the results of the treatment to find out what part each played in the success or failure of that treatment.

When the sulfonamides and the antibiotics first became available, the senior author pointed out the difficulties of appraising a chemotherapeutic agent in the treatment of surgical infections which formerly required a surgical procedure for their control and cure (22). At that time it was stated that if the use of a drug obviated surgery or permitted a limited procedure when a radical one would ordinarily be indicated, if it definitely shortened healing time or caused a rapid disappearance of the causative organism, or if it permitted a primary closure or an earlier successful secondary closure than would ordinarily have been expected, the favorable role of the drug would have to be acknowledged.

As in our previous studies with penicillin (23) and bacitracin (24, 26), the cases have been divided into four groups according to the result obtained. Results were called "excellent" if the infection came under control within 72 hours. The response in these cases was often surprising in its rapidity and indicated a rapid cessation of activity of the invading organisms. If the response was definite but somewhat slower in its manifestation, the results were called "good." When it could not be certain that the drug had played any role in the subsidence of the infection, the cases were put in the "questionable" group. This includes patients receiving only a few doses of the drug. When it was obvious that the infection went on its way notwithstanding bacitracin treatment, the drug was listed as having "no effect."

Results obtained. The over-all results of treatment are shown in Table IIIa. If the "excellent" results and the "good" results are

called favorable, it is seen that favorable results were obtained in 78 per cent of these cases. In the prophylactic cases none are listed as "excellent" because infection does not usually establish itself within 72 hours and the effect of the drug could not be judged until the case had gone on to complete healing.

Surgical infections in contrast to medical infections are characterized by the local breakdown of tissue or the local exudation of leucocytes. In using antibiotics in their treatment, the opportunity is often given to apply the drug not only systemically through the blood stream, but also locally at the main focus of infection. This was true in 117 cases in this series (Table IIIb). The results were excellent in 23 of these cases and good in 70, which is 80 per cent favorable. In the other 43 cases, bacitracin was administered by intramuscular injection without any local application at the principal focus of infection. Eighteen of these gave an excellent response and 13 good, for a total of 72 per cent favorable results. These two groups do not represent parallel or comparable series. In the cases in which bacitracin was given systemically only, there was generally no breakdown of tissue and so the favorable results were more prompt in their manifestation. On the other hand, in the cases which received the combination of systemic and local treatment, the good results outweighed the excellent results by more than 3 to 1.

It is the authors' experience that whenever possible bacitracin should be used locally as well as systemically because one is then able to apply the drug in close contact with the causative organisms and in a much higher concentration than could otherwise be obtained. This is particularly true in neurosurgical infections. Yet it is seen that bacitracin, even in the small doses which are used with safety by intramuscular injections, is able to overcome infections which are operative at a distance from the site of injection.

One hundred and five of the 131 established infections were treated with bacitracin as the only antibiotic, when once it had been started. The results were favorable in 84 per cent. The other 26 had bacitracin combined with other antibiotics with a 61 per cent favorable response. Some of the combinations were used because the cultures indicated a mixture of organisms not entirely covered by bacitracin, while in other cases the other agents were added when bacitracin failed to control the infection. However, in 6 out of the 8 cases treated with bacitracin and penicillin, a synergistic action was demonstrated between the two antibiotics and in 5 of these the results were favorable. Six out of the 8 prophylactic surgical cases also received other drugs because of operations on the intestinal tract where contaminants other than those susceptible to bacitracin were to be expected. Among 21 prophylactic neurosurgical cases, 15 patients received penicillin intramuscularly along with the bacitracin, but only bacitracin was used locally in the brain or on the meninges because bacitracin is so much less toxic to brain tissue than is penicillin.

Clinical categories. When these groups are broken down according to the clinical diagnoses, we find that the largest group among the surgical cases comprises 11 infected operative wounds and 10 cases of chronic osteomyelitis, the majority of which gave a favorable response to bacitracin. Several of the smaller groups were particularly responsive, namely, 6 cases of undermining burrowing ulcer, 6 cases of bacterial synergistic gangrene and 3 cases of gas gangrene. Altogether 36 different clinical categories of surgical conditions were treated and favorable results were obtained in 76 per cent, as shown in Table IVa, which includes the prophylactic cases as well as the established infections. In the related medical infections (see Table IVb) there were favorable results in 88 per cent. This high score is due to the fact that 13 of these cases were instances of recurrent erysipelas all occurring in the same person. Reference will be made to this patient later in the discussion. In the neurosurgical group, including the prophylactic cases as well as the established infections, 43 cases are shown in Table IVc with favorable results in 74 per cent. The frequency of susceptible organisms and the almost complete lack of toxicity of bacitracin for brain and nerve tissues would seem to make it worth while to consider bacitracin as the drug of choice in most neurosurgical infections.

TABLE IVa.—RESULTS OF BACITRACIN THERAPY ON THE BASIS OF CLINICAL GROUPS

Surgical Infections*

Diagnosis	Total No. cases	Results of treatment			
		Excellent No. cases	Good No. cases	Questionable No. cases	No effect No. cases
Infected operative wound	11	1	7	3	0
Chronic osteomyelitis	10	3	5	2	0
Undermining burrowing ulcer	6	1	4	1	0
Bacterial synergistic gangrene	6	3	3	0	0
Cellulitis	5	3	0	1	1
Infected accidental wound	5	3	1	1	0
Peritoneal abscess	5	2	3	0	0
Ulcer of leg or foot	4	1	2	1	0
Gas gangrene	3	1	2	0	0
Abscess of liver	3	0	1	0	2
Miscellaneous (2 cases of each)†	18	3	9	6	0
Miscellaneous (1 case of each)‡	9	2	4	3	0
Prophylactic	8	0	7	0	1
Totals	93	23	48	18	4

Favorable results in 76 per cent of cases

*28 different clinical categories.
†Including decubital ulcers, infected compound fracture, acute osteomyelitis, granuloma gangrenescens, abscess of breast, multiple infected sebaceous cysts, deep abscess, diabetic gangrene of foot, scrotal gangrene.
‡Including tetanus, acute lymphadenitis, infected pilonidal cyst, dacryocystitis, sinusitis, infected epithelioma of skin, general peritonitis, multiple lung abscesses, multiple abscesses of abdominal wall.

TABLE IVb.—RESULTS OF BACITRACIN THERAPY ON THE BASIS OF CLINICAL GROUPS

Related Medical Infections

Diagnosis	Total No. cases	Results of treatment			
		Excellent No. cases	Good No. cases	Questionable No. cases	No effect No. cases
Recurrent erysipelas*	13	12	1	0	0
Endocarditis	4	0	3	0	1
Postoperative pneumonia	3	1	2	0	0
Miscellaneous (1 case of each)†	4	0	2	1	1
Totals	24	13	8	1	2

Favorable results in 88 per cent of cases

*All attacks in the same patient.
†Including Behcet's syndrome, pemphigus, cavernous sinus thrombosis, sinusitis.

TABLE IVc.—RESULTS OF BACITRACIN THERAPY ON THE BASIS OF CLINICAL GROUPS

Neurosurgical Infections

Diagnosis	Total No. cases	Results of treatment			
		Excellent No. cases	Good No. cases	Questionable No. cases	No effect No. cases
Meningitis	7	2	4	1	0
Brain abscess	5	0	3	0	2
Infected craniotomy wound	5	1	4	0	0
Infected laminectomy wound	2	1	1	0	0
Osteomyelitis of skull	2	1	1	0	0
Epidural abscess	1	0	1	0	0
Prophylactic	21	0	13	6	2
Totals	43	5	27	7	4

Favorable results in 74 per cent of cases

Duration of infection. Table V shows the results in the 131 established infections according to the duration of illness before the administration of bacitracin. Thirty days were taken arbitrarily as the dividing line between acute and chronic infections. The acute cases were placed in two groups, the first of which were treated promptly with bacitracin within the first 4 days of the illness. With the others, treatment with bacitracin was delayed for one reason or another from 5 to 30 days from the onset of the illness. It is seen that favorable results were obtained in 88 per cent of the 34 cases treated in the first 4 days. The rest of the acute group yielded 81 per cent in 43 cases, while in the 54 chronic infections the favorable response fell to 72 per cent. It is also seen that in the early group the response was excellent in 21 cases and good in about half that number, whereas in the acute infections of longer duration the excellent results were only one-fourth as many as the good results. Among the chronic infections there were still 13 which responded promptly within the first 72 hours, but this was only half of the number which were placed in the "good" category.

Previous treatment. Ninety-seven, or almost three-quarters of these 131 cases, had had previous treatment which had failed to bring the infection under control. All but 3 of the 97 had had penicillin either alone or with one or more other antibiotics, including strepto-

mycin, aureomycin, chloromycetin, terramycin, or one of the sulfonamides. In the 34 cases which had had no previous treatment, the results were favorable in 91 per cent and almost twice as many were placed in the "excellent" as in the "good" column. The results in the group which had had previous treatment were only 75 per cent favorable. This difference may be due largely to the fact that those which had had no previous treatment were treated earlier in the course of the illness than the others, while those which had had first one and then another antibiotic without a favorable response, dragged on into the more chronic stages of illness when there was often necrosis of tissue or physiological disturbances represented by anemia and protein and electrolyte imbalance. Furthermore, in the cases of longer duration secondary contaminants often came into the picture causing synergistic action with the primary invaders. It is seen in Table VI, however, that although 27 cases failed to respond to penicillin, 9 of those cases gave an excellent response to bacitracin and 16 a good response, for a total of 93 per cent favorable cases. Cases which had received penicillin in addition to from 1 to 3 other antibiotics without success, showed a progressive decline in favorable results, except for the small group of 7 cases which had had all kinds of treatment and yet all of them were favorable in their response to bacitracin.

TABLE V.—RESULTS OBTAINED IN 131 ESTABLISHED INFECTIONS ACCORDING TO THE DURATION OF SYMPTOMS BEFORE BACITRACIN THERAPY

	Duration in days	Total No. cases	Results of treatment				
			Excellent No. cases	Good No. cases	Per cent favorable No. cases	Questionable No. cases	No effect No. cases
Acute infection	1– 4	34	21	9	88	4	0
Acute infection	5–30	43	7	28	81	7	1
Chronic infection	over 30	54	13	26	72	9	6
Totals		131	41	63	79	20	7

Bacteriology. Naturally, in any study of surgical infections the causative organisms and the secondary contaminants are of primary importance and interest. Some of the secondary contaminants are able to invade the local tissues and the body as a whole. Others not invasive themselves may act as synergists and thus potentiate the primary invaders, while still others are simply there as saprophytes and multiply in the presence of destroyed tissue which serves as their pabulum. The results of bacitracin therapy according to the bacteria cultured in this series of cases are shown in Table VII. This includes 186 different strains of organisms, some in pure culture and others mixed. It is seen, as was the case in the previous reports on penicillin (23) and

TABLE VI.—RESPONSE TO BACITRACIN IN 34 PREVIOUSLY UNTREATED CASES AND THE RESULTS IN 97 ESTABLISHED INFECTIONS WHICH FAILED TO RESPOND TO OTHER ANTIBIOTICS

Systemic therapy	Total No. cases	Results of treatment					
		Excellent No. cases	Good No. cases	Per cent favorable*	Questionable No. cases	No effect No. cases	Per cent Unfavorable
Previous treatment: Penicillin only	27	9	16	93	1	1	7
Penicillin plus 1 other antibiotic	19	5	9	74	5	0	26
Penicillin plus 2 other antibiotics	22	3	11	64	6	2	36
Penicillin plus 3 other antibiotics	19	2	8	53	5	4	47
Penicillin plus 4–6 other antibiotics	7	1	6	—	0	0	—
Treatment other than penicillin	3	1	2	—	0	0	—
Totals	97	21	52	75	17	7	25
No previous treatment	34	20	11	91	3	0	9
Totals	131	41	63	79	20	7	21

*Percentages not figured for less than 10 cases.

TABLE VII.—RESULTS OF BACITRACIN THERAPY ACCORDING TO THE BACTERIA FOUND BY CULTURE

Organisms	Total incidence No. cases	Results of treatment				
		Excellent No. cases	Good No. cases	Per cent favorable	Question-able No. cases	No effect No. cases
Hemolytic streptococcus, pure	2	0	2	100	0	0
Hemolytic streptococcus, mixed	12	4	6	83	2	0
Nonhemolytic streptococcus, pure	1	0	1	100	0	0
Nonhemolytic streptococcus, mixed	13	6	7	100	0	0
Staphylococcus aureus, pure	44	8	26	77	8	2
Staphylococcus aureus, mixed	35	10	17	77	7	1
Anaerobic or microaerophilic cocci, pure	6	3	2	83	0	1
Anaerobic or microaerophilic cocci, mixed	14	4	8	86	2	0
Clostridium welchii, pure	0	0	0	—	0	0
Clostridium welchii, mixed	5	4	1	100	0	0
Gram-negative rods, pure	0	0	0	—	0	0
Gram-negative rods, mixed	31	9	15	77	6	1
Others, pure	5	2	1	60	2	0
Others, mixed	18	6	8	78	4	0
No growth from cultures	4	0	2	50	0	2
Culture not taken	20	14	5	95	1	0
Total cases, pure	58	13	32	78	10	3
Total cases, mixed	49	14	24	78	9	2
Total cases with no culture or no growth	24	14	7	88	1	2
Totals of cases	131	41	63	79	20	7

bacitracin (26), that a large number of these infections were caused by a mixture of organisms. In this series of 131 established infections, pure cultures were obtained in only 58 cases. In 49 there were mixtures of organisms and in 20 no cultures were taken. In 4 no growth was obtained from the specimens. Organisms were seen on stained smears of the exudate, but they failed to grow with the method of cultivation employed, although the cases were unquestionably infections, possibly anaerobic. The 20 cases in which no culture was taken included the 13 instances of recurrent erysipelas in which the infectious agent was almost certainly a hemolytic streptococcus, and where it was not possible to obtain a culture without local injection of the tissues, which seemed to be unnecessary and unwise. The other cases were for the most part those in which the inflammation was diffuse, as in cellulitis and postoperative pneumonia, and in which it did not seem possible at the time to obtain a culture. In such cases treatment has to be to some degree guesswork. The favorable results obtained in these cases does not nullify the dictum that cultures should be obtained whenever possible.

It is seen in Table VII that favorable results were obtained just as often in the mixed infections as in the pure infections. This was true in the previous bacitracin study (26) in contrast to the results obtained in the penicillin study (23). The same thing is true when the pure and mixed infections are broken down into each of the main bacterial species groups. This may be explained by the fact that bacitracin not only has a wide range of activity over the invasive organisms, but is not inhibited (as is penicillin) by any substance like penicillinase, which is so often produced by secondary contaminants not of themselves invasive organisms.

The largest single group are the staphylococci most of which were coagulase-positive. This is the only group which occurred more often in pure than in mixed cultures, and yet it is seen that the favorable results were the same in both instances. The favorable results with the anaerobic and microaerophilic cocci are particularly noteworthy. It is of considerable interest and importance that the Welch bacilli and the gram-negative rods were never found in pure culture. The Welch bacillus is, of course, often locally invasive and kills by producing a powerful toxin in the local area of its activity. An unexpected finding was the high incidence of good results in the cases yielding gram-negative rods, which are ordinarily resistant to bacitracin except in high concentrations. It should be noted again that these only occurred in mixed infections. In some of these cases they must have been there simply as surface growing organisms which were either held in check by the concentration of the local bacitracin or yielded to another antibacterial agent used in conjunction with the bacitracin when the laboratory tests or the clinical course indicated that this should be done.

Bacterial resistance and susceptibility. In the Laboratory for Bacteriological Research of the College of Physicians and Surgeons particular attention has been paid to the tests for sensitivity of the organisms to penicillin and bacitracin. These tests have been carried out by one of us (B.A.J.) in almost all of the cases in this series treated in the Presbyterian Hospital. They were done with 136 of the 186 cultures obtained and were not done with 50 strains recovered for the most part from patients treated in neighboring hospitals which did not have the facilities for these tests.

Inasmuch as 94 of the 131 cases of established infection had failed to respond previously to penicillin with or without other antibiotics, it was important to know whether this was due to the fact that the organisms were primarily resistant or had developed a resistance to penicillin during the course of ineffective treatment or whether the lack of success could be assigned to some other cause. When a similar study was carried out in the previous series (26), it was found that 122

TABLE VIII.—SENSITIVITY OF THE ORGANISMS TO PENICILLIN AND BACITRACIN

Organisms	Total incidence No. cases	Sensitivity* PS BS No. cases	PS BR No. cases	PR BS No. cases	PR BR No. cases	NO TEST No. cases
Hemolytic Streptococcus †	14	4	0	10	0	0
Nonhemolytic streptococcus	14	4	0	9	1	0
Staphylococcus aureus	79	22	0	37	6	14
Anaerobic or microaerophilic cocci	20	7	0	4	0	9
Clostridium welchii	5	1	0	1	0	3
Gram-negative rods	31	0	0	0	23	8
Others	23	1	1	0	5	16
Totals	186	39	1	61	35	50

*PS—Penicillin sensitive
PR—Penicillin resistant
BS—Bacitracin sensitive
BR—Bacitracin resistant
†Not grouped. See text

cultures of all kinds were susceptible to both bacitracin and penicillin, 104 were susceptible to bacitracin but resistant to penicillin, and 11 were resistant to bacitracin but susceptible to penicillin. Ninety-two were resistant to both, most of these being gram-negative rods which are only susceptible to these antibiotics when they are present in very high concentration. In the present study (Table VIII), only 39 were susceptible to both, while 61 were resistant to penicillin and susceptible to bacitracin. Only 1 was susceptible to penicillin and resistant to bacitracin. (This was a Bacillus subtilis present in a mixed culture and was probably of no clinical significance.) Of the 61 cases resistant to penicillin, 49 had had penicillin during the early stages of the infection. Twelve patients did not have previous penicillin during the present illness, although they may have had it on some previous occasion.

Additional evidence of the efficacy of bacitracin. An analysis of the results presented would seem to indicate clearly that bacitracin has improved therapeutic procedure in the care of surgical infections. This is further supported by the following facts: In 18 of the 131 cases of established infections, surgery was completely obviated in conditions which ordinarily would have required a surgical procedure to

control the infection. In 1 other case the surgical procedure was of a very limited extent. In 22 of the cases an immediate primary closure was done after excision of the infected tissue. Seven of these received a primary skin graft. In 7 cases a secondary closure was possible earlier than it would ordinarily have been expected, 5 of these being closed by skin grafts.

Toxicity of bacitracin. With our own confidence in the efficacy and safety of intramuscular bacitracin restored by the experience with the last 100 of the cases in the series previously published (26), the authors were anxious to continue a detailed study of the subsequent cases so treated in order to see if that confidence was justified and to determine whether the wider use of systemic bacitracin by other doctors might be recommended.

Observations have been made on the 160 cases in this second series with particular reference to daily urine examination, to biweekly studies of the blood urea nitrogen or nonprotein nitrogen, and to the clinical symptoms of loss of appetite, nausea and vomiting, in order to determine whether these evidences of toxicity could be correlated with the LD50 figures obtained by the Food and Drug Administration for the lots of bacitracin which were employed. With all of these factors considered, the cases have been divided into the same three groups from the point of view of toxicity, which were used in the previous study. In the first group the symptoms and signs were slight or mild. In the second group they were moderate and transient. In the third group they were disturbing.

In 15 of the 160 cases more than one lot of bacitracin was used. Two lots were employed in 14 of these cases and four lots in the other. This case was treated over a considerable period of time. In 9, the number of the lot used was not recorded. The evidences of toxicity were attributed to each lot used in any given case. The data, therefore, are for 177 case lots. The manifestations of toxicity of the different manufactured lots employed have been studied.

In approximately two-thirds (68 per cent) of the cases, evidences of nephrotoxicity were slight or mild, often disappearing with continued treatment. In 30 per cent they were moderate but transient and gave no concern, usually diminishing during continued treatment and disappearing as soon as treatment was stopped. In both of these categories the nephrotoxicity may be called inconsequential.

In only 4 cases (2 per cent) were there any disturbing symptoms of toxicity. With 2 of these cases the appearance of a considerable amount of albumin made it seem advisable to stop treatment. One of these patients (Series No. 1146) was in a neighboring hospital and could not be directly under the care of the senior author (F.L.M.), so that when albuminuria developed, those in charge of the case deemed it advisable to discontinue systemic bacitracin. One of these cases (Series No. 1214), a 2 month old infant, may have had a dose four times larger than was intended. The signs of toxicity disappeared slowly but completely in both of these patients. In another young patient, a boy of 6 (Series No. 1182), an oliguria developed on the fourth day and a shutdown was threatened. The blood urea nitrogen rose alarmingly. However, as soon as bacitracin was stopped, he responded to treatment and after 4 days the blood urea nitrogen fell and the albuminuria receded. Recent tests, a year and a half later, show no albumin and a normal blood urea nitrogen. The fourth disturbing case (Series No. 1176) was a man with multiple liver abscesses, who showed no apparent response to 7 days of treatment with bacitracin. Other antibiotics were reemployed to no avail. When he died 2½ months later, death was preceded by a rising blood urea nitrogen. Autopsy showed healed liver abscesses, but a "bile nephrosis" and kidney damage to which bacitracin may have contributed although one cannot be certain of this.

These last 2, which were the only very disturbing cases, had been treated with the same lot of bacitracin with an LD50 of only 372 ± 28, considerably below the desired specification. This lot was used with some misgiving on that account. Two other cases treated with this lot developed a rash and all 7 of the patients complained of more than the usual amount of pain at the site of injection. When these manifestations of toxicity appeared, the lot was withdrawn from any further systemic administration and 2 cases still being treated

were given another lot with prompt disappearance of the toxic signs.

Table IX gives a correlation between the LD50 as determined by the Food and Drug Administration and manifestations of disturbing toxicity. The trivial and transient have been combined because they are inconsequential. Among 21 cases with an LD50 range from 275 to 421 units for 20 gram mice, 1 case threatened a kidney shutdown and another revealed kidney changes at autopsy 2 months later, which might have been due to bacitracin. This gives a disturbing toxicity percentage of 9.5. Among 141 cases treated with lots having an LD50 range from 455 to 702 there were only 2 disturbing cases in which it was thought best to stop the treatment. This incidence of disturbing toxicity is 1.4 per cent. Although these differences are not statistically significant, they are in line with the results reported in the previous study (26). Together they indicate the wisdom of widening the margin of safety by requiring an LD50 of 500 units for bacitracin intended for intramuscular administration, in order that it can be used without hesitation whenever it is indicated.

TABLE IX.—DEGREE OF NEPHROTOXICITY FOLLOWING INTRAMUSCULAR ADMINISTRATION OF BACITRACIN IN RELATION TO THE LD50 AS DETERMINED BY THE FOOD AND DRUG ADMINISTRATION

F.D.A. LD50 limits per 20 gm. mouse	Total No. cases	Trivial and transient No. cases	Toxicity prolonged and disturbing No. cases	Per cent disturbing
275–421 units	21	19	2	9.5
455–702 units	141*	139	2	1.4

*Omitting 6 cases treated with lots tested by the manufacturer but not by F.D.A., reported as having LD50 of more than 500.
Totals exceed the number of cases treated because some received bacitracin from more than one lot. In such instances the toxicity was assigned to each lot. In 9 cases the numbers of the lots were not recorded.

ILLUSTRATIVE CASES

The following case reports will illustrate many of the points brought out in the presentation of data:

CASE 1. Series No. 1085, R. G. This 21 year old boy had had sores on the mucous membrane of the mouth and various places on the skin, particularly the genitals, for over 10 years. A diagnosis had been made of Behcet's syndrome. He had had many kinds of therapy, including penicillin, the sulfonamides, vaccines, moccasin venom, and various ointments and antiseptics, all to no avail. Cultures of the skin lesions yielded a Staphylococcus aureus and a nonhemolytic streptococcus susceptible to bacitracin and penicillin. He was given bacitracin in a dosage of 9,700 units every 6 hours intramuscularly. Bacitracin solution was applied locally to the mouth ulcers and bacitracin ointment to the skin lesions. Two days after initiating treatment, the purulent exudate diminished and the ulcers all showed signs of healing. However, on the third day, the patient became nauseated and vomited once. Nausea continued next day, so the treatment was stopped, but more lesions promptly developed. He was then given a course of aureomycin, but it had no effect. Penicillin was also tried again but without avail. He was therefore put back on 10,000 units of bacitracin every 8 hours and again promptly began to improve. He left the hospital on the ninth day of treatment and continued the systemic bacitracin at home with the same dosage without toxic symptoms. This was continued for 3 months. During the last month he received 20,000 units every 12 hours. It was then stopped for 10 days and the lesions became active again. Bacitracin was readministered in a dosage of 20,000 units every 12 hours for 5½ months. This permitted him to carry on his normal activities. Thus, over a period of 10 months, he received a total of 10,500,000 units of systemic bacitracin. During this time his blood urea nitrogen never went above normal and he showed only 1 plus albumin from time to time in the urine. During the past 22 months local bacitracin has kept the infection under control. There has been no sign of nephrotoxicity.

This case illustrates the prolonged use of systemic bacitracin without significant nephrotoxicity.

CASE 2. Series No. 1132, A. C. This Columbia football player sustained an abrasion of the leg during football practice. Four or 5 hours later there was marked swelling of the leg, which gradually began to stiffen and throb. The tibia was tender throughout its extent and a diagnosis of acute osteomyelitis was made. He was given 300,000 units of crysticillin every 3 hours, but showed no improvement. On the third day he was admitted to the hospital with a high fever and high blood count. The right leg was greatly swollen and there was tenderness all along the tibia. There was a small abrasion on the anterior surface of the leg, which was obviously infected. Cultures were taken which showed a Staphylococcus aureus, which was resistant to penicillin but susceptible to bacitracin, but when one-fifth of each of the inhibiting doses of penicillin and bacitracin were combined, they prevented the growth of the organism in vitro. With the failure to respond to penicillin alone, bacitracin was added to the treatment in a dosage of 20,000 units every 8 hours. The whole process then promptly began to subside. There was marked improvement in the

next 24 hours and within 48 hours the temperature reached normal. The whole process subsided so rapidly that the patient was able to leave the hospital in a week and felt well enough on the day of discharge to go and see the football game. On the following week he was permitted to play.

This was a very striking example of the synergistic action of penicillin and bacitracin.

CASE 3. Series No. 1135, L. S. Nine months before admission to the Presbyterian Hospital this patient was thrown from a car and suffered a compound fracture of the left forearm just above the wrist. The doctor wished to amputate but the patient refused, so the doctor did his best to save the hand. The wound became infected in spite of débridement and two courses of penicillin and aureomycin. The hand gradually took a flexed position and the wound continued to discharge large quantities of pus from 3 sinuses. Culture yielded a pure Staphylococcus aureus resistant to penicillin but susceptible to bacitracin. The x-ray film revealed a very bad right-angle deformity with several sequestra and abundant callus (Fig. 1). An abscess cavity was found between the flexor tendons and the bone. All diseased bone and the head of the ulna were removed and the hand was put up in a dorsiflexed position. The wound was then flooded with bacitracin solution containing 1,000 units per cubic centimeter, tamponed with China silk and packed with gauze wet with bacitracin. The packing was changed daily. During the 20 day period of hospitalization the patient received 20,000 units of bacitracin intramuscularly every 8 hours. The wounds promptly became clean and one by one healed by granulations. The silk tampon was removed on the tenth day, when 2 small bone fragments were removed. These must have been left at operation. During the course of healing, 2 other small fragments of bone were extruded. Thereafter the wound healed promptly. Fibrous union developed between the radius and the carpus. A bone graft may be required later, but the patient is satisfied for the present and with the aid of a leather brace reinforced by a metal band, she has a very useful hand (Fig. 2). The urine on admission showed no albumin or casts, and the albumin only went up to 1 plus for 7 out of the 20 days of systemic bacitracin treatment. A few casts appeared, but there were never any red cells and only a few white cells and epithelial cells in the urine. The blood urea nitrogen before bacitracin was started was 11 milligrams per cent and never rose above 13 milligrams per cent.

This case illustrates the control of an extensive osteomyelitis of long duration by the appropriate surgical procedure augmented by the administration of the appropriate antibiotic.

CASE 4. Series No. 1218, B. P. This 39 year old woman had a supracervical hysterectomy and bilateral salpingo-oophorectomy for multiple fibroids of the uterus. In spite of 400,000 units a day of procaine penicillin given as a prophylactic, she had a sudden rise in temperature on the seventh day and the roentgenogram revealed atelectasis or atypical pneumonia. The penicillin was increased to 600,000 units every 6 hours. Aureomycin and dihydrostreptomycin were added to the antibiotic therapy. During the next 12 days the chest findings remained static, while abdominal signs, particularly distention and right lower quadrant tenderness, became prominent. In spite of this the patient had daily bowel movements and very little vomiting. An x-ray film of the abdomen revealed an extraordinary amount of free air or gas in the peritoneal cavity (Fig. 3). In the absence of localizing signs, she was treated conservatively with the antibiotics mentioned. On the thirteenth day of infection, one of us (F.L.M.) was called in consultation and advised immediate operation. When the abdomen was opened, it collapsed like a balloon. A generalized peritonitis was found with a plastic fibrinous exudate over the surface of the liver, the ascending colon, the cecum, the appendix, and the lower ileum. No perforation could be found, but it could not be certain that the original focus of infection was not the appendix, which had perforated and then sealed off. The amount of gas present could hardly have been produced by the bacteria found on culture, which yielded a hemolytic streptococcus, susceptible to bacitracin but resistant to penicillin, streptomycin and terramycin, and a nonhemolytic streptococcus and a pyocyaneus, resistant to all of them. There was no evidence of a break in the pelvic suture line and the process seemed to be entirely independent of the previous operation. The appendix was removed. Twenty thousand units of bacitracin in 100 cubic centimeters of saline were sprayed over the surface of the abdominal contents. Penrose drains were placed into the pelvis, the appendiceal region and the right lumbar gutter, and brought out through the lower end of the wound. She was given 20,000 units of bacitracin intramuscularly every 8 hours and terramycin 500 milligrams every 6 hours postoperatively, but the latter was stopped when the organisms were all reported resistant to it. With all of that infection in the peritoneal cavity, it was thought that she would surely die, but following operation she did extremely well, except for a period of disorientation lasting from the third to the sixth day. This was due possibly to withdrawal of alcohol to which she had become habituated, and it was relieved by the administration of alcohol in small quantities. Thereafter recovery was uneventful. All symptoms and signs of peritonitis were gone by the end of the first week. There was no rise in the nonprotein nitrogen during treatment. Two plus albumin was present before bacitracin was started and this fell to 1 plus during the course of treatment. An occasional granular cast was found in

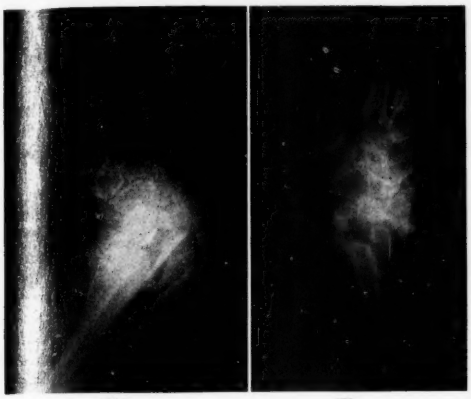

Fig. 1. Fig. 2.

Fig. 1. Case 3. The extent of osseous infection, deformity and malposition on admission.

Fig. 2. Case 3. Position of useful function after removal of focus and control of infection 3½ months after operation.

the urine. After 10 days bacitracin was reduced to 10,000 units every 8 hours and was continued for another 14 days. This was an extraordinary recovery and can certainly be attributed to the bacitracin, which was active against the chief pathogen in a mixture almost certainly of intestinal origin.

This case demonstrates that bacitracin may be introduced into the peritoneal cavity without toxic symptoms and that it can overcome a generalized peritonitis.

CASE 5. Series No. 1203, W. K. Ten days before admission this boy cut his left index finger with a sickle. It bled profusely and he went to his local doctor, who cleansed the wound and closed it by suture. He gave the patient tetanus antitoxin but no antibiotic. Two days later the finger became swollen and painful. The doctor removed the stitches, but the inflammation did not subside. He was given penicillin, but it had no effect and the edges of the skin wound gradually became necrotic. Cultures showed a heavy growth of Welch bacilli. Wet dressings were applied, but the infection continued to spread and necrosis of the skin extended outward in all directions. Local trimming of the dead skin did not bring the infection under control. The boy is a clarinet player and was greatly disturbed about the possibility of interference of this avocation from the loss of a finger. On admission, there was some swelling of the proximal phalanx of the left index finger and the contiguous portion of the hand. On the radial side of the finger there was an ulcer extending down to the periosteum of the middle phalanx and overlapping the middle interphalangeal joint

Fig. 3. Case 4. Extraordinary amount of free air or gas in the peritoneal cavity before operation.

proximally and the distal joint distally. Anteriorly it extended almost to the midline, exposing the flexor tendon sheath but not the tendon itself. The surface of the ulcer was covered with a grayish exudate and some superficial slough. Cultures were taken, which revealed Clostridium welchii susceptible to bacitracin, only slightly susceptible to penicillin, and resistant to streptomycin, also a nonhemolytic streptococcus susceptible to bacitracin but resistant to the other two, and Escherichia coli susceptible to streptomycin. He was given 10,000 units of bacitracin every 8 hours intramuscularly and local bacitracin was applied on China silk to the surface of the wound in a concentration of 1,000 units per cubic centimeter. This was kept moist by covering it with zinc oxide ointment gauze. Dressings were changed daily. Systemic bacitracin was continued for a week and local bacitracin for 12 days. After the third day, when the culture revealed a contaminating colon bacillus, streptomycin and sulfamylon were added to the local bacitracin, being mixed with it in equal parts. There was never any extension of the process. Clostridium welchii was present for only 2 days after the treatment was started. The wound rapidly cleaned up. On the fifth day the cultures showed no growth. Granulations rapidly appeared all over the surface of the wound. He was sent home and the wound was grafted about 2 weeks later. The urine showed a transient albuminuria and cylindruria, which promptly disappeared as soon as treatment was dis-

Fig. 4. Case 6. Healed skin flap after delayed primary closure.

continued. During treatment the blood urea nitrogen fell from 19 to 13.5 milligrams per cent.

This case illustrates the prompt control of a gangrenous mixed infection containing Clostridium welchii by systemic and local bacitracin and the addition of other appropriate medication, when indicated by culture reports.

CASE 6. Series No. 1216, G. P. Fifteen months before admission this patient had sustained a chemical burn of the hand from a combination of nitric and sulfuric acids in glass containers. A typical burn resulted all over the dorsum of the hand, but it was not realized until later that a small piece of glass, which cut the extensor tendon, had penetrated the hand in the region of the middle metacarpophalangeal joint. An abscess formed in the region and several attempts were made to bring this infection under control by surgery. The piece of glass came out after one of these operations, but the wounds continued to drain. During the course of the next year the finger became increasingly stiff and because of the probability of a useless finger, even if the infection could be controlled by removal of the infected tissues, he was advised to have an amputation. It was found that the dorsal surface of the middle metacarpal bone was involved in the infectious process. The cut ends of the tendon were not exposed and had become sealed off. Cultures revealed a hemolytic Staphylococcus aureus, resistant to penicillin but susceptible to bacitracin, streptomycin, and terramycin. The finger was amputated, including the head of the metacarpal bone, and a long anterior flap was left, utilizing the skin over the proximal and middle phalanges of the finger. The wound was tamponed with China silk after being flooded with bacitracin solution containing 1,000 units per cubic centimeter. Packing wet with the same solution was used within the silk tampon. He was also given 10,000 units of bacitracin every 8 hours intramuscularly. There was no exudate whatsoever. The wound remained clean and on the second postoperative day the culture showed no growth. On the third day, therefore, a late primary closure was done by bringing up the anterior skin flap and suturing it to the dorsum of the hand. The wound healed by primary union without any evidence of infection. The patient left the hospital on the ninth postoperative day with the wound clean and all stitches out (Fig. 4). Systemic bacitracin was continued every 8 hours for the whole period of his hospital stay. There were no clinical signs of nephrotoxicity. The blood urea nitrogen was 11.5 milligrams per cent before bacitracin was started and did not go above 16.5 milligrams per cent.

This case illustrates the possibility of a late primary closure of a wound after excision of the infected tissue, when accompanied by the systemic administration and by the local application of bacitracin. The negative culture on the second postoperative day indicated that the wound closure would be successful.

CASE 7. Series No. 1200, G. G. This patient had had a series of staphylococcal infections in the form of furuncles and carbuncles for a number of years. One of these developed in the usual manner on the back of the right calf, but the lesion did not heal in the usual way and gradually took on the characteristic appearance of the progressive bacterial synergistic gangrene, gradually spreading out in all directions, destroying the skin, with the characteristic outer zone of erythema, middle raised purple necrobiotic zone, and inner zone of "suede leather" gangrene. As it spread outward, it left behind a granulating surface. The infection did not respond to penicillin, aureomycin, dihydrostreptomycin or terramycin. The patient was seen by one of us (F.L.M.) on the twenty-first day of the infection (Fig. 5). Bacitracin ointment had been used locally for a few days before that, so that surface cultures yielded no growth. It was obviously not reaching the spreading periphery of the lesion. However, with the intramuscular injection of 10,000 units of bacitracin every 8 hours, the infection promptly came under control. The necrotic skin readily

Fig. 5. Case 7. Characteristic appearance of progressive bacterial synergistic gangrene before systemic bacitracin therapy.

Fig. 6. Case 7. Complete healing by residual epithelium left by the spreading infection, obviating radical excision or skin grafting.

separated from the living tissues, the raised purple region flattened out, and new skin began to grow from residual islands of epithelium and from the margin. This went on to complete and rapid healing without the necessity either for excision or for skin grafting (Fig. 6). The urine showed a transient albuminuria and an occasional cast, but the blood urea nitrogen did not change during treatment.

This case illustrates the rapid and complete control of synergistic gangrene by means of bacitracin administered systemically in a relatively small dosage, after penicillin, aureomycin, terramycin and dihydrostreptomycin had failed to cure the infection. This is the seventh consecutive example of this clinical entity which has responded to bacitracin, and adds weight to the belief that bacitracin at the present time is the antibiotic of choice in the treatment of this disease.

CASE 8. Series No. 1241, M. Z. This 9½ month old infant came into an urban hospital in a semi-coma with a fever of 105 degrees, a purpuric rash all over his body, a stiff neck, bulging fontanelle, and twitching of the hands and facial muscles. He had been treated with penicillin and sulfadiazine 3 months before for a meningococcus meningitis with apparent success. There had been no intrathecal treatment at that time. It was evident that he had a recurrent meningitis. Spinal fluid showed a high cell count and gram-negative diplococci. He was given both penicillin and sulfadiazine for 11 and 14 days, respectively. On the eighth day streptomycin was added intramuscularly and on the eleventh day chloromycetin was also given both orally and rectally. This combination of antibiotics with the sulfonamide had no effect. The high temperature, convulsions, and coma continued. Bacitracin was called for and was started on the nineteenth day after admission, 1,000 units being given intrathecally for 13 days. It was also given intramuscularly for a period of 15 days in a dosage of 1,875 units (about 400 units per kilogram of body weight) every 8 hours. The temperature fell abruptly to normal and did not rise above 100.2 degrees thereafter. After the eighth day of treatment the temperature was perfectly normal. There was residual weakness of the right arm, but this began to improve at once. When treatment began there was considerable evidence of kidney involvement from the infection itself. The blood urea nitrogen was 79 milligrams per cent at the time bacitracin was started, but on the third day thereafter it fell to 19 milligrams per cent and on the next day to 12 milligrams per cent. The urine showed 1 plus albumin before bacitracin therapy, but showed only a faint trace during treatment. It was completely normal when the baby left the hospital 9 days after systemic bacitracin was discontinued. Six weeks after discharge the baby appeared normal, both mentally and physically, except for slight weakness of the arm.

This case illustrates the success of bacitracin treatment in a severe case of meningococcus meningitis, which had failed to respond to a combination of penicillin, streptomycin, chloromycetin, and sulfadiazine, and with a rapid

clearing up of the kidney disturbance caused by the infection itself.

Discussion. This series of cases covers clinical entities seen every day in general surgical and neurosurgical hospital practice. The authors are fully aware of the fact, however, that in one respect at least, this series does not represent the ordinary run of general surgical and neurosurgical infections, in that many of them were referred to us only because they were serious and resistant problems of infection and had failed to respond to other methods of therapy. Many of the cases had received indiscriminate antibiotic therapy without preliminary bacteriological studies to determine the causative organisms and their susceptibility to the available antibiotics. This is brought out in the illustrative Cases 1 to 8. Almost three-quarters of these 160 patients had failed to respond to the treatment first employed. The detailed stories of some of the patients in this series, who have gone from one doctor to another and from one hospital to another over a period of months or years, are almost incredible.

The astute clinician may have some clew as to the causative organism when he makes his diagnosis, but he cannot be certain of its susceptibilities to antibiotics without the aid of a bacteriology laboratory which has the facilities to carry out these tests. Treatment without such tests is largely guesswork. However, any hospital which has an operating room for surgical procedures should be equipped for this service. The patient is not getting the full benefit of our knowledge unless cultures are taken at the earliest opportunity and the proper antibiotic or combination of antibiotics employed, as indicated by the laboratory study. For the benefit of the patient it is more important to determine the susceptibility of the organisms than to determine their species. If that is done, the patient will usually respond quickly to treatment and will be spared prolonged illness with temporary or permanent disability and sometimes death. Prolonged illness often results in the economic exhaustion of the patient and his family.

In acute infections the attending doctor does not have to await the results of the laboratory tests before starting treatment with the antibiotic which in his judgment is most likely to meet the situation, but when the results of the test come through, he should modify his treatment accordingly, if it is demonstrated that he has not started with the most effective medication.

The high proportion of favorable results in this series is therefore indicative of the efficacy of bacitracin. This should encourage others to employ it more frequently and earlier than heretofore. Some readers may think that we have been too sanguine in determining the results. We believe, however, that we have been conservative. Certainly those results classified as "excellent" could hardly be questioned, because the benefit was so rapid and obvious. There might be a difference of opinion about those classified as "good," because control of the infection was more slowly attained. By the same token there could be a difference of opinion when the results were "questionable." Some of these patients may have benefited by the drug.

To give some indication whether or not we have claimed too much for bacitracin, it might be worth while to consider the causes of failure or our reasons for placing the cases in the two unfavorable groups. Of the 26 questionable cases, there were 10 in which the infection was caused or secondarily contaminated by organisms not susceptible to bacitracin. In another 6 of these cases the period of treatment was too short for evaluation. In 4 others there was an inadequate surgical removal of diseased tissue. In 3 there was primarily a favorable response, but this was followed by a relapse. In 2 cases there were too many antibiotics used for a proper evaluation of any one of them. In 1 case the patient was almost moribund before the treatment was started.

In the 10 cases in which there was obviously no effect from the drug, 4 were practically moribund or the disease was too far advanced with irreparable damage to vital organs. In 2 cases the disease was caused by organisms not susceptible to bacitracin. In 2 there was no adequate explanation for the lack of effect. In 1 case there was inadequate surgery and in 1 there was a plastic foreign body which required removal.

The group of medical cases related to surgical practice, which was considered in this series, gives no idea of the benefit which might be derived from systemic bacitracin in medical infections in general, to which it has not yet been widely applied. However, Reimer's report on a series of pneumonias and reports on several cases of endocarditis (1947) are encouraging.

The 13 instances of recurrent erysipelas were all in the same person. She had the first attack in the right arm following postoperative radiation for a mammary carcinoma. Sulfadiazine and penicillin had been effective with the earlier attacks, but in the more recent recurrences they had both failed to stop the infection. For that reason, bacitracin was called upon and the response was immediate. Attacks recurred 13 times over a period of 24 months. During one of these attacks she was away from home and penicillin was again used without effect. She returned home at once and again bacitracin brought the infection to a standstill. Of particular interest is the fact that with these 13 courses of treatments, the patient has shown no signs or symptoms of toxicity, the urine has shown no albumin, and she has developed no allergic manifestations.

The endocarditis cases in this series had all failed to respond either to penicillin or to streptomycin, but 3 of these cases immediately began to improve when bacitracin was started and the latest reports indicate that there has been no recurrence of symptoms. The single failure was a case of staphylococcal septicemia with a somewhat uncertain diagnosis of endocarditis. There seemed to be no clinical improvement over a period of 8 days of bacitracin treatment. It was discontinued when coincident symptoms of a pulmonary infarct suddenly developed, but these symptoms were not blamed on the bacitracin. Five subsequent blood cultures were negative but the patient continued to run a fever and when last heard from, his condition remained unchanged.

The neurosurgical cases will be reported in more detail in other publications. The striking response to bacitracin in cases which have failed to be controlled by penicillin and the absence of any toxicity from the drug when it is introduced into the cerebral ventricles or into cavities left after operations on the brain or when given by lumbar puncture, suggests that it should be the drug of choice and the one primarily used when the causative organisms are susceptible to it, even though they may also be susceptible to penicillin. The difficulty of both bacitracin and penicillin to pass the blood-brain barrier and enter the brain substance when given intramuscularly, suggests that the local instillation of the drug is more important than the intramuscular use of it in neurosurgical infections. However, when the meninges are inflamed, bacitracin reaches them through the blood stream when given intramuscularly. The combined treatment is therefore indicated in these cases (Case 8).

The excellent results obtained when bacitracin is given within the first 4 days of illness, as in Case 2, would seem to warrant its earlier employment in the future than in the past. This will undoubtedly be done more often, if cultures are taken early and the susceptibility of the organisms is tested for all of the antibiotics, and if it is known that bacitracin of low toxicity is available.

The antibiotics should never be used indiscriminately, either in combination as a "shotgun" remedy or one after another, if the first fails to accomplish the purpose. It is true that penicillin and streptomycin are relatively cheap, but the bacteriological studies are also cheap and if hospital expenses, both those paid for by the patient and those supplied by hospital endowment, can be cut down by the earlier administration of the proper antibiotic or combination of antibiotics as determined by the culture studies, the better it will be for all concerned. With the proper treatment no infection should fail to come under control within 5 to 15 days and should never go on to a chronic stage, as was the case in more than one-third of the cases in this series.

The bacteriological studies which reveal a mixture of organisms in many instances, indicate clearly the importance of determining as soon as possible the causative and associated organisms and applying the antibiotic or combination of antibiotics indicated. It would seem that hemolytic streptococcal infections are playing a much less important role than they did before the days of the sulfonamides

and penicillin. Formerly they were of equal importance with staphylococcal infections. In this series staphylococcal infections predominate and that is the only group in which there are more pure than mixed cultures. Many of these failed to respond to penicillin or to the other antibiotics until bacitracin was given. The reason for failure seems to be largely in the steadily increasing resistance of staphylococci to penicillin (Cases 2 and 3). This would seem to indicate that the availability of another bactericidal agent, bacitracin, which is highly potent against the staphylococci, should be called upon early to fill the gap in therapy, if penicillin fails or if the test shows a resistance of the organism to penicillin and a susceptibility to bacitracin.

Since in discussing the reaction of bacteria to antibiotics the terms "susceptible" and "resistant" are relative only, it is necessary to define what is meant by such terms in any given report. The figures presented in Table VIII represent the results of sensitivity tests by the blood agar plate filter paper disc method. The unitage of the antibiotics used to moisten these discs was adjusted for each antibiotic so that there would be no zone of inhibition of growth adjacent to the disc, if the resistance of the organisms was 10 to 15 times that of the so-called "standard strain." No attempt was made at quantitative determinations. If there was a definite clear zone of inhibition, no matter how narrow, the strain was reported as sensitive; if there was no zone, it was reported as resistant. However, in cases in which it was deemed necessary or desirable to use any particular antibiotic in the treatment of an infection, if our test showed the organism to be resistant or on the borderline, the more exact quantitative broth assay test was carried out. In these broth tests, strains which were resistant to high concentrations of the individual antibiotics were often susceptible to combinations of pencillin and bacitracin in fractional doses, demonstrating a synergistic action between the two antibiotics (16).

Unfortunately, Lancefield groupings of the hemolytic streptococci recovered from this series of cases were not done. It is our opinion that the resistant strains of hemolytic streptococci reported here, as in Case 4, did not belong to Group A. A review of the beta hemolytic streptococci recovered from cases of impetigo and ecthyma over a 4 year period from cultures sent by the Dermatological Services of the Columbia-Presbyterian Medical Center showed no instance of such a streptococcal strain having been reported as resistant to penicillin. In the majority of our strains reported as resistant, the nature of the infection and the associated bacteria point to fecal contamination as the possible source of the infection. The beta hemolytic strains of the enterococcus all belong to Lancefield Group D and this group in our experience has shown considerable resistance to penicillin.

With regard to the nephrotoxicity of bacitracin, it is evident from this study that if the dose is kept below 100,000 units a day with material now available, disturbing symptoms and signs will occur in not over 2 per cent of cases and sufficient warning will be given either by clinical manifestations or by urinary examination to stop treatment, if necessary. If material with an LD_{50} of 500 units for a 20 gram mouse is used consistently, the untoward reactions should be evident in less than 1 per cent. Favorable clinical results are usually obtained with 50,000 to 60,000 units a day. It must not be forgotten that when penicillin was first available, favorable results were obtained even in severe cases of septicemia with doses of 40,000 units a day. Somewhat later Lyons stated that his experience with penicillin in staphylococcal infections indicated that 200,000 units a day might be required (21).

The only untoward effect of bacitracin anywhere in the body seems to be a swelling of the epithelium of the convoluted tubules of the kidney, resulting in albumin in the urine with granular casts and white blood cells and in a few cases renal epithelial cells and red blood cells. Blood flow through the kidneys and both tubular and glomerular filtration are retarded by large doses of bacitracin. Glomerular injury is secondary and only present with excessive amount of the drug (27, 29). However, these effects are almost invariably temporary and readily reversible, and the good that is accomplished by control of the infec-

tion certainly far outweighs the harm that is done.

It is well recognized that patients differ from one another in the degree of kidney irritation with the same dosage of bacitracin, probably because of varying previous trauma to the kidney. Our 2 most disturbing cases showing nephrotoxicity were both hemolytic streptococcal infections with albumin in the urine before the administration of bacitracin. However, it would seem that the effect of bacitracin on the kidneys may be different from the usual causes of kidney disturbance, because the 32 patients who showed albumin in the urine before the administration of systemic bacitracin, did not show any higher incidence of toxicity from bacitracin than the 68 cases which had not previously shown albumin. Case 8, outlined previously, had albuminuria and a high blood urea nitrogen before bacitracin and these signs returned promptly to normal under bacitracin therapy.

There can be no doubt that when the deep-tank method of preparing bacitracin was first used, for some reason not yet determined, it produced material which was clinically more toxic than that which was produced by surface growth. However, surface-growth bacitracin is no longer available. Fortunately, in the past year, the product made by the deep-tank method has been steadily increasing in purity. The units per milligram have increased and the toxicity has decreased. This of itself suggests that the toxicity may not be inherent in the antibiotic but in some impurity. Two other manufacturers are now producing bacitracin in deep tanks and the product of all three of these firms now meets the specification which we consider safe for intramuscular use. With further work by the manufacturers, it may be possible to raise this specification further, thus increasing the margin of safety.

The LD50 test, as at present carried out by the Food and Drug Administration, has a wide margin of error and the results obtained by the manufacturers are often at variance. The most likely cause of this is the variation of resistance and susceptibility of different strains of mice. The test itself requires further standardization. For the present it must serve as a safety test for the protection of the patient.

SUMMARY

1. Our latest experiences with local and systemic bacitracin therapy have been reviewed.

2. The rationale and technique of local application have been presented with an outline of 4 illustrative cases.

3. One hundred and sixty more cases treated systemically with bacitracin by intramuscular injection, with or without supplementary local administration at the site of infection, have been studied and the data have been analyzed. Eight of these cases have been briefly summarized.

4. One hundred and thirty-one of the whole series were established infections. In the other 29 cases bacitracin was used prophylactically when infection was anticipated.

5. About three-fourths of the cases of infection had failed to respond to other antibiotic treatment when bacitracin was called for. All but 3 of 97 cases had had penicillin either alone or with another antibiotic.

6. The over-all results of therapy were favorable in 78 per cent of the cases. In those which had had no previous treatment the results were favorable in 91 per cent. In those previously treated unsuccessfully with penicillin and/or other agents, favorable results were obtained in 72 per cent.

7. Evidences of kidney toxicity were absent or mild in 68 per cent of the cases, moderate and transient in 30 per cent, and disturbing in only 2 per cent. Symptoms and signs of toxicity usually subsided with continued treatment and almost invariably disappeared as soon as treatment was discontinued.

8. It would seem, therefore, that we have demonstrated that bacitracin is an effective drug without serious toxicity, if material is used for systemic administration which meets a specification of LD50 of 500 units for a 20 gram mouse and if the dose is kept below 100,000 units a day. Satisfactory control of infection can often be obtained by half that amount.

9. In neurosurgical infections bacitracin may often be the treatment of choice for both local and systemic administration.

10. The importance of prompt determination of the causative and associated organ-

isms and tests for their susceptibility to the available antibiotics is stressed. Then and then only can the proper antibiotic or combination of antibiotics be administered at an early stage of the infection and the patient be saved from prolonged illness and disability and economic exhaustion.

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THE DOUBLE ONLAY BONE GRAFT IN THE TREATMENT OF DELAYED UNION AND NONUNION

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SINCE MacEwen in 1880 first successfully transplanted bone from one person to another, bone graft surgery has made remarkable advances. The double onlay bone graft has come into common usage only in the past few years. It was first emphasized in modern times by Boyd in 1941 for congenital pseudarthrosis, but very little appears in the literature until 1948. Albee, in his comprehensive book on bone grafts republished in 1940, lists no less than 25 different types of grafts but he does not once mention the use of the double onlay.

The demand for a large piece of bone undoubtedly has been a limiting feature in the development of this type of grafting, but the advent of bone banks will certainly give impetus to the use of this procedure. Although in all of the cases to be reported autogenous bone was used, the few objections to the double onlay have since been overcome by the institution of a bone bank. The cases done with homogenous bank bone have been followed for too short a period of time to be included in this study, but they will form the basis for a future communication.

The problem of the fate of the bone graft has been reviewed thoroughly in the recent literature and deserves only brief mention here. Wilson has recently contributed excellent studies on the fates of autogenous and refrigerated homogenous bone. The evidence that all bone grafts die, as propounded by Gordon seems to be based on a carryover from the certainly dead fate of the os purum or os novum originally used in bone grafting. These bones were dead to begin with and certainly contained no osteogenic properties. We adhere rather to the "creeping substitution" process expounded by Phemister and advanced by Abbott. The cases to be presented have shown early attachment of the graft to the host. However, it is believed that a very long graft may lose considerable strength and that the osteogenesis or replacement in grafts covering large defections may take many years or may never be completed. This point will be illustrated in a case in the text in which a united graft covering a 4 inch defection, fractured with minor trauma 1½ years after its application. It is interesting to note that the fracture site of the graft healed despite degeneration of the proximal portion of the graft.

Our sole indications for the use of the double onlay graft have been delayed union and nonunion. We have found this method applicable to delayed union and nonunion of the tibia and humerus. The source of autogenous bone has been the tibia for the graft and the iliac bones for chips.

This type of grafting has many distinct advantages over other types:

1. The fixation at the fracture site is stronger and more complete than the single onlay intramedullary or any lesser graft. This was well demonstrated by Bateman who showed that it required 196 pounds hanging weight to fracture a double onlay graft as compared to 90 pounds for a single onlay and 52 pounds for an inlay.

2. The availability of osteogenic activity is greater. The two endosteal surfaces provide excellent sources of osteogenesis.

3. The framework of the double onlay acts as a shored up structure and a form for the packing of cancellous chips from which we can expect the greatest regeneration of bone. This is not so with single grafts or plates.

4. The technical aspects must be considered. Every detail of good bone surgery must be adhered to. However, the accom-

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plished surgeon experienced in handling trauma cases of today will find the technical difficulties minimal.

. A minimal amount of metal is necessary. Only four metal screws are used.

There are objections to the double onlay graft:

. The removal of a large segment of normal tibia to provide a graft is hazardous and fractures and postoperative infections have been reported. Also, we have roentgenograms showing that tibiae, from which a graft had been taken 8 years prior, have not yet replaced the removed bone. This objection is obviated by use of bank bone.

. A large bulk of graft is necessary and may impair circulation. In our experience, we have encountered no circulatory problems nor lymphedema. The use of relatively thin grafts and proper placement away from subcutaneous areas will obviate this objection.

3. The procedure is time consuming and requires three open reductions—one at the fracture site, one at the donor site, one for chips. The use of homogenous bank bone eliminates two open operations and cuts operating time to approximately 1 hour.

TECHNIQUE

The skin over the fracture area and donor site are prepared for 24 hours with a tincture of green soap and alcohol preparation, or more recently a hexachlorophene preparation. Rigid no-touch technique is employed throughout. We have found the dividing line method of the instrument tray effective. A red line is drawn across the center of the instrument tray so that the working end of an instrument always lies on one side and the handle on the other. In this manner, hand contamination of the wound is averted when instruments are reintroduced.

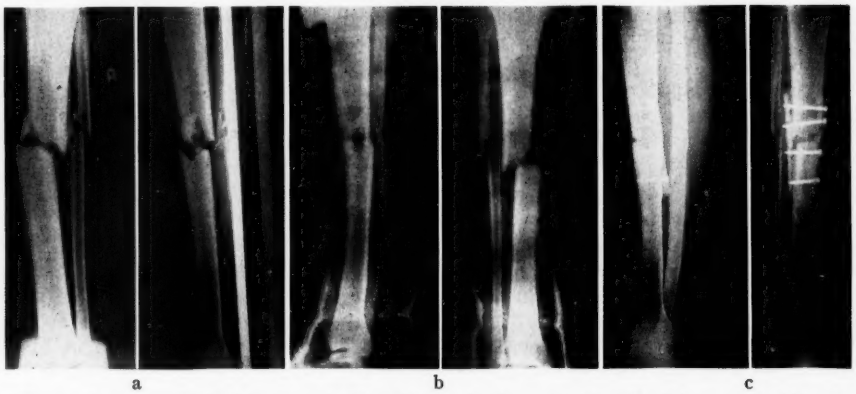
Two operating teams are employed. The first exposes the fracture site, excises devitalized tissue, and removes eburnated bone ends and sequestra, if present. The recipient site is then prepared by leveling the bone with a chisel. Careful trimming and fitting of the grafts and bone ends for intimate and secure application are imperative. At a given time, the donor team starts to work and removes the graft from the tibia, the size of which has already been determined. This same team is responsible for the removal of cancellous slabs from the ilium. In our more recent cases in which bank bone was used, the necessity for this second team has been obviated.

In general, the graft is 5/8 inch wide and is removed with a slowly rotating motor driven saw. In the autogenous grafts, the periosteum is not stripped. In our opinion each graft should be no less than 2¾ inches long to avoid undue torque which may occur in shorter ones. We have used grafts as long as 5½ inches.

In all instances, the graft is fixed with 4 Sherman SMo 18.8 screws, using only the coarse thread type. We aim at 1/8 inch protrusion of the screws through the distal graft. The screws are never countersunk as in plating, but merely made "thumb tight." These screws are not removed at a later date unless they should give symptoms, but thus far such occasion has not arisen. In the form provided by this method, cancellous chips are then packed tightly; cortical bone is never used. In the closure of the wound, no local medicaments are used and we do not hesitate to provide a skin graft if we fear tension in the wound closure. An appropriate circular plaster cast or spica is applied. Short preoperative discussions and assignment of duties remove the delays ordinarily found in multiple team procedures.

CASE REPORTS

CASE 1. See Figure 1. D. P., aged 23 years, male. The patient was admitted on October 24, 1949 after an automobile accident. Aside from other injuries, he sustained a transverse comminuted fracture of the middle third of the right tibia and fibula. He was treated by skeletal traction with a wire through the os calcis for a period of 2 weeks. The leg was then placed in a circular cast to the mid-thigh. The cast was reapplied at intervals and after 9 months there was no evidence of union. A double onlay bone graft with cancellous chips from the ilium was performed, and the leg immobilized in plaster for a period of 6 months. Weight bearing was begun with the aid of a walking caliper and roentgenograms showed evidence of bony union 6 months after operation. The patient is now able to walk well without support.



a b c

Fig. 1. Case 1. a, Original fracture. b, No evidence of union 9 months after injury. c, Double onlay bone graft with chips; end result demonstrating union at 6 months.

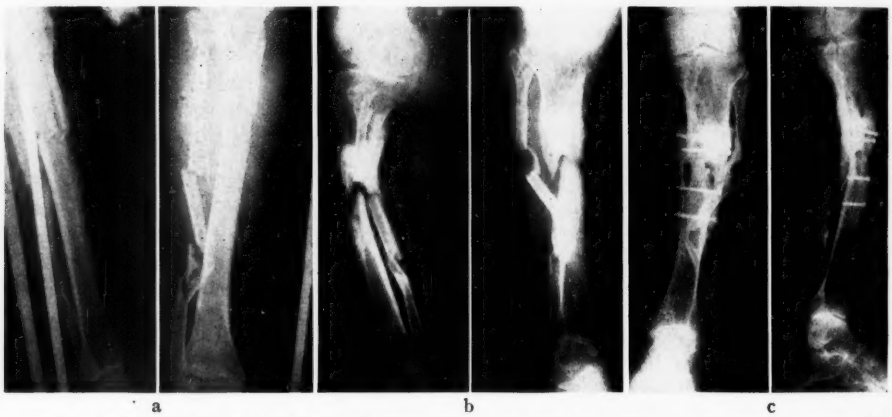


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Fig. 2. Case 2. a, Original fracture. b, Nonunion after 19 months. Several sequestrectomies and Orr dressings have been done. c, Eighteen months post grafting. Bony union and weight bearing without support.

CASE 2. See Figure 2. G. G., aged 35 years, male. The patient was admitted on September 26, 1947 after an automobile accident. He was critically ill with head injury and fractures of several long bones. Because of his poor condition, he was merely immobilized in splints for 1 week. The fracture we are concerned with was an open comminuted fracture of the right tibia and fibula which (after 1 week in splints) was treated by skeletal traction, using a wire through the os calcis. The patient developed a severe psychosis and had to be transferred to a mental hospital. He developed an osteomyelitis of the right tibia. His mental condition improved after several months and he was returned to us for further treatment. This consisted of Orr dressings and several sequestrectomies and saucerizations. Finally his tibial infection subsided and treatment of the nonunion became necessary. On April 28, 1949, nineteen months after injury, a double onlay bone graft with chips from the ilium was performed, and the limb was immobilized in plaster. After 8 months' immobilization, a walking iron was added and weight bearing begun. At 12 months after grafting, the cast was discarded when roentgenogram showed union. The patient wore a caliper brace for 6 months, but is now able to walk well without support.

CASE 3. A. S., aged 74 years, male. The patient was admitted on December 2, 1949 after an automobile accident in which he sustained fracture of the left tibia and fibula at the junction of the lower and middle thirds. He was treated by Kirschner wire traction through the os calcis. Weights were varied to accommodate for distraction, overriding, and bowing. On January 15, 1950, he was placed in a plaster cast and the wire removed. Repeat roentgenograms over a period of 8 months revealed no

a b c

Fig. 3. Case 4. a, Original fracture. b, Nineteen months post injury. Plate removed and chips from ilium inserted at 10 months. No union 9 months later. c, Fourteen months post double onlay bone graft. Union and weight bearing without support.

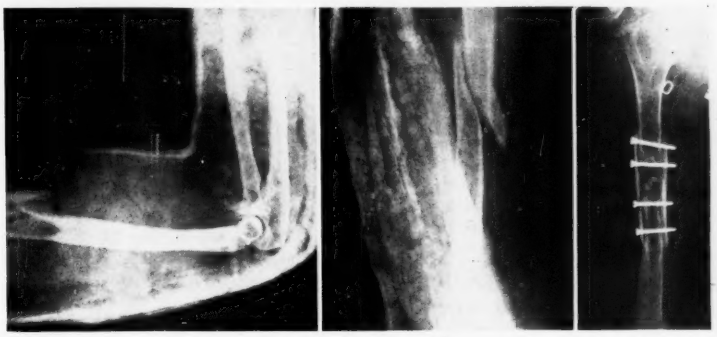

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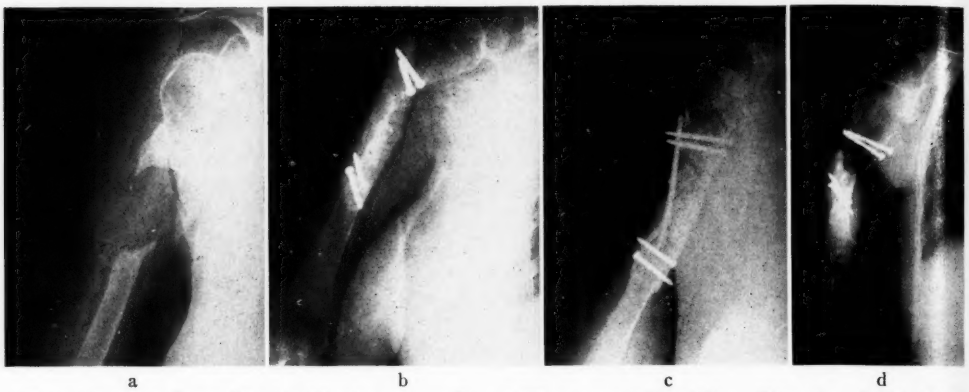
Fig. 4. Case 5. a, Original fracture in hanging cast. b, Removal of hanging cast. Nonunion 8 months post injury. c, End result, union and full restoration of function at 6 months after double onlay bone graft.

union. On July 24, 1950, a double onlay bone graft plus chips from the ilium was performed. Follow-up roentgenogram showed union after 7 months of immobilization in plaster. The patient is now able to walk without support.

CASE 4. See Figure 3. E. Mc., aged 69 years, female. The patient was admitted on September 26, 1948 after an automobile accident. She sustained an open fracture of the upper third of the left tibia, aside from other injuries with which we are not concerned. This fracture was treated by traction with a wire through the os calcis for a period of 3 weeks, at which time the limb was immobilized in plaster. On December 23, 1948, three months post injury, an open reduction and internal fixation with a six hole Sherman plate and screws was performed because of failure of union. Over the course of the next 7 months, it was noted that the fragments were separated 3 millimeters and union did not occur. The plate and screws were removed and bone chips from the ilium packed between the ends of the fragments. Follow-up for the next 9 months revealed no evidence of union, and a double onlay bone graft with chips from the ilium was performed. The patient was immobilized in plaster for a period of 6 months and is now able to walk without support.

CASE 5. See Figure 4. A. C., aged 39 years, female. The patient was admitted on March 19, 1949 after a fall. She sustained a fracture of the right humerus at the junction of the middle and upper thirds. She was treated with a hanging cast for a period of 3 months, with failure of union and unsatisfactory position. An open reduction with internal fixation by two screws was performed, and still union did not occur. On June 28, 1950, fifteen months after the injury, a double onlay bone graft from the tibia and bone chips from the ilium was performed. The patient was immobilized in a shoulder spica for



a b c d

Fig. 5. Case 6. a, Large defection following osteomyelitis of open fracture. b, Seventeen months post grafting. c, Eighteen months post grafting. Fracture of the graft. d, Three years post grafting. Disruption of graft. Note that union of the graft occurred at the site of fracture in the graft.

a period of 3 months at which time the spica was removed and active and passive motion instituted. This patient has had union and almost complete restoration of function.

CASE 6. See Figure 5. H. E., aged 55 years, female. This patient sustained a fracture of the right humerus at the junction of the middle and upper thirds on October 19, 1942. The exact details of her original treatment are obscure, but we do know that she had two open reductions with screws within a period of 2 days. Apparently the second was performed following failure of the first procedure to engage the fragments. The patient subsequently developed an osteomyelitis and 6 months following the original injury she was admitted to this hospital for treatment. The screws were removed as was a piece of involucrum. The patient was treated for osteomyelitis by several surgical procedures. On December 17, 1944, twenty-six months post injury, an intramedullary graft from the tibia was done and the patient was immobilized in plaster. Two months later this graft was fractured and proceeded to degenerate. The patient accepted her disability and remained with a flail relatively useless limb. On July 2, 1948, six years after the original accident, the patient was admitted to this hospital and a double onlay bone graft from the tibia with bone chips from both ilia was performed. The defect necessary to bridge was approximately 4 inches. She was immobilized in a plaster spica for 9 months, at which time active and passive motion was instituted. The patient became able to abduct and flex her upper arm. She was able to sew, write, comb her hair, and carry on activities which had been impossible prior to grafting. Just prior to presentation at a conference, while having the roentgenogram made, the graft was heard to snap and the roentgenogram revealed fracture of the graft. This occurred at 1½ years following the graft. Unaware of this occurrence the patient was not immobilized and a follow-up 1 year later revealed degeneration of the graft, but union at the site of the fracture in the graft.

DISCUSSION

The academic consideration of what constitutes a delayed union and when in time it should be termed nonunion is an absorbing one. However, it is our belief that if union in a long bone does not occur or give evidence of occurring within a 4 to 6 months' period, it should be treated as though it were a nonunion. It is true that patience may be rewarded by eventual union in another 6 months to 2 years. However, a fair percentage will remain ununited and we will still be faced with further procedures and further disability in terms of a year or more. It is our firm conviction that a bone without evidence of healing in 6 months will not show sudden union in the next month or two, but we can almost always count on union with a double onlay graft in 3 to 6 months. Except in cases of infection, it is unreasonable to wait 1½ years before terming a case a nonunion and then look forward to further treatment. The academic fact that union may occur if one waits long enough has been established, but practically no case should be allowed to remain without adequate treatment to prove the fact further.

With the advent of bank bone, we may have to change more of our concepts and al-

ady, fresh fractures are being plated with homogenous bone and chips instead of metal plates. We believe that a double onlay should be instituted in delayed union much before we are able to term a fracture a true "nonunion." Our first and longest waiting period in this series was 4 years; our shortest and most recent waiting period was 8 months.

The problem of length of immobilization has been a source of concern. We have set a minimum period of 6 months of adequate immobilization for the tibia and 3 months for the humerus, but are guided to a great degree by roentgenographic findings. In our first case and our only failure, we had the unfortunate experience of a fracture of the graft 1½ years after application. This patient had a 4 inch bone defection in the humerus and was immobilized for 9 months in a shoulder spica. She then was able to carry on housework, comb her hair, write and sew, things she could not do before. Just prior to presentation at a conference, a roentgenogram was made and, while abducting her arm, the technician heard the graft snap. Unfortunately the patient was not aware of the fracture immediately and returned home; hence, there was no immobilization. However, examination 1 year later showed healing of the fracture site of the graft, but due to torque and lack of immobilization the proximal portion of the graft disintegrated. She still retains some improved function over her pregraft status, but certainly her case should be considered a failure. We remain with the question as to whether immobilization for 2 or 2½ years is necessary in this type of case and whether it is sociologically and economically feasible. At any rate this case points out well the failure of complete replacement of bone in large defections over a relatively long period of time. The quality of immobilization is important, and adequate full plaster casts must be applied. Casts must be changed, but never lessened until union occurs. Fracture at the time of change of cast is a distinct danger and must be guarded against.

Adequate mobilization of all free joints, and subsequently those which are fixed, calls into play every detail of the methods of rehabilitation.

a b

Fig. 6. a, Defect from donor site of intramedullary graft 6 years after removal (Case 6). b, Donor site for graft 7 months following removal (Case 4).

The other 5 patients are all doing well; 4 with fractures of the tibia are walking without the aid of braces or supports. Postoperative pain, edema, and circulatory disturbances have not occurred. There has been no osteomyelitis nor wound infection despite the fact that in 2 cases nonunion occurred following osteomyelitis. The use of antibiotics is a great comfort, but we cannot reiterate strongly enough the necessity for maintaining rigid operating technique.

SUMMARY AND CONCLUSIONS

1. The double onlay bone graft is advocated for treatment of delayed union and nonunion due to its greater strength, greater possibility for osteogenesis, the construction of a form for bone chips and its ease of technical accomplishment.

2. Six cases of double onlay bone graft using autogenous bone are presented, with 1 failure in a large defection due to fracture of the graft which occurred 1½ years after application.

3. Principles of operating technique are outlined.

4. The results with double onlay bone grafts warrant its use early in the course of a delayed union rather than reserving it as a method of last resort.

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THE PHYSIOLOGICAL MECHANISM FOR DEATH IN MASSIVELY BLEEDING PEPTIC ULCER

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PHYSIOLOGICAL precepts upon which the immediate therapy of gastroduodenal bleeding can rest are as yet unestablished. At the present time, the choice between medical and surgical therapy rests mainly on a statistical rather than on a rational basis. There is no unanimity of opinion as to how a massively bleeding peptic ulcer should be treated. Those adhering to nonoperative therapy point to a statistical reduction in the incidence of mortality in medically treated patients as compared to surgically treated cases.

Similarly, there is disagreement about the use of transfusion. Some believe that blood transfusion should be minimal or completely withheld to prevent any rise in blood pressure to normal levels which might possibly dislodge a poorly adherent blood clot in the opened vessel. Others feel that the bleeding must be treated vigorously with blood transfusions.

A majority now hold that surgery should be undertaken in selected cases. This belief is based on the statistical analysis of clinical data. But even this majority cannot agree upon the basis for the selection of operative cases. It is a general impression that before one considers surgery the bleeding must be of sufficient magnitude to endanger life. Few clinicians have made accurate blood volume measurements, with the result that the extent and rate of bleeding in fatal cases remain unknown. For this reason alone, most of the clinical cases are incomparable and valid conclusions can seldom be drawn. Again, unless unequivocal evidence exists that the blood replacement has been adequate in both surgically and medically treated cases, deductions made from the comparison of such groups are invalid. It would obviously be best to operate only in those cases which would otherwise be fatal. Toward this end, there is information which aids in the selection of some of the more lethal cases. There is no question but that the mortality is highest in the age group over 45 years. The rate of bleeding may be roughly estimated clinically by the response to transfusion. Nearly all observers agree that the continuation of bleeding over a prolonged period, or lack of improvement with medical therapy, is an indication for surgery. By the same token, cessation of bleeding would seem to offer a contraindication to surgery; and yet, fatal bleeding is often intermittent. Severe hemorrhage in a patient with a definite history of peptic ulcer, repeated hemorrhage, massive bleeding occurring during the course of medical therapy, profuse bleeding associated with constant pain, hemorrhage occurring with perforation, excessive bleeding in the presence of pyloric stenosis all have been offered as indications for surgery. More recently, Stewart has used blood volume studies and red cell mass determinations to assess the magnitude of bleeding. Those patients who have had a reduction in excess of 2.5 million red blood cells per cubic millimeter or 60 per cent of the red cell mass are scheduled for operation. The real clinical problem is to determine how massive the bleeding really is, since there is a growing opinion that all massively hemorrhaging ulcers should be treated surgically.

Many of the indications for surgery mentioned were based upon the observation of fatal cases, which implies that the circumstances upon which the prognosis was based became apparent only when it was too late. Therapy determined by a knowledge of the physiological alterations which occur in this condition should be more fundamental than an indirect statistical approach.

Clinical observation suggests that blood loss per se cannot be responsible for the not infrequent fatal outcome, since blood replace-

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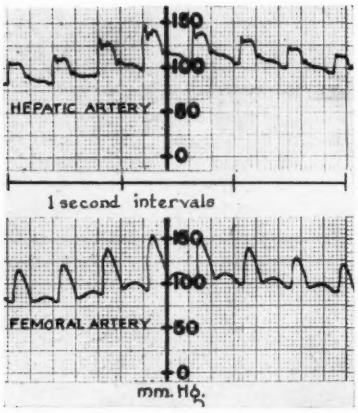

Fig. 1. The prebleeding hepatic and femoral pulse pressure tracings are shown. The hepatic artery pulse pressure is above. The steep ascending portion marks the beginning of the ejection phase which after reaching a peak falls to a well marked dicrotic notch. Notice the gentle plateau falling slowly to the next peak. In the subcutaneous femoral artery pulse pressure tracing shown below, there is a well marked diastolic plateau.

ment, even though massive and maintained and seemingly adequate, does not forestall the eventual development of shock and death. For this reason, surgery, if contemplated, must be performed early. According to Finsterer, surgery which is postponed as late as 48 hours after the onset of bleeding is likely to be followed by a mortality. This observation suggested to the author that a difference exists between the effects of hemorrhage of gastroduodenal origin and hemorrhage from other sites.

Because the hepatic artery proper, the gastroduodenal artery, and the right gastric artery are branches of the hepatic artery, a large opening into any one of these should instantly reduce the rate of blood flow through the other branches. The hydrodynamic changes involved may be illustrated by the following situation: a man is watering his garden when suddenly a large hole is cut into the middle portion of the hose. The flow at the nozzle of the hose immediately drops to a drizzle.

The cause of massive hemorrhage from a duodenal ulcer is erosion into the gastroduodenal artery or one of its major vessels. This vessel is extremely vulnerable because it lies immediately posterior to the first portion of the duodenum. Hemorrhage from a gastric ulcer usually originates from the right or left gastric arteries. Massive gastroduodenal hemorrhage should therefore produce a greater reduction in blood flow through the hepatic artery than would be produced by an equal hemorrhage from other noncontiguous arteries. Conversely, hemorrhage from a peripheral vessel or other visceral arterial trunk would effect no greater reduction in blood flow through the hepatic artery than would be uniformly exhibited elsewhere in the vascular tree.

Our experiments were designed so that hemodynamic changes could be measured simultaneously in both the femoral and the hepatic arteries. The effects of hemorrhage of gastroduodenal artery origin could then be compared with the effects of a peripheral artery hemorrhage.

EXPERIMENTAL METHODS AND MATERIAL

The investigations were conducted as acute experiments on large sized dogs. The bleedings were done in various ways to simulate human conditions. Rapid bleedings were performed with normal blood pressures, and bleedings were also done when the blood pressure had already reached hypotensive levels. Continuous bleeding and replacement were done. A tracing of blood pressure (or pulse pressure) and blood flow were made simultaneously from one femoral artery and the hepatic artery during the course of the bleeding. The site of hemorrhage was the contralateral femoral artery or the gastroduodenal artery.

After surgical exposure of the vessel a cannula was placed in the cut end of the artery and the blood conducted to a graduated cylinder by means of a plastic tube. This procedure produced a rapid hemorrhage equivalent to dividing the artery and preventing it from retracting. Blood replacement and infusions were administered via the intravenous route. All experiments were done under nembutal anesthesia.

In those experiments wherein pulse pressure curves were sought, the hepatic artery was ligated and divided and the pressure tracing made from the central cut end. No attempt

was made to measure blood flow in these experiments. Pulse pressure tracings could not be made simultaneously with blood flow tracings since the method used by us to measure blood flow distorts the pressure curves.

In the several experiments in which blood flow and blood pressure were measured, a femoral artery and the hepatic artery were divided and both proximal and distal ends of the vessel were cannulated. The blood was then made to run through the flowmeter before returning to the distal cut end. The flowmeter introduces but little increase in the total resistance and the measurements of flow are quite accurate.

Blood flow was measured with an electromagnetic rotameter (12), and blood pressure (or blood pressure tracings) with a Sanborn electromanometer. The simultaneous recordings were made on a Sanborn four channel polyvisocardiette. In some earlier experiments, blood pressure recordings were made with a mercury manometer and recorded on a smoked drum. No attempt to measure blood flow was made in the early experiments. In all, a total of 12 successful experiments were performed. Although there were minor variations in anatomy and vessel size, the records in all experiments were uniformly similar.

RESULTS

Prehemorrhage pulse pressure tracings taken from the hepatic and femoral arteries are illustrated in Figure 1. Notice that the pulse wave arrives at the hepatic artery 0.04 second sooner. The hepatic pulse wave shows a sustained systolic peak. The entire ejection phase lasts 0.16 second and falls only 25 millimeters to a well marked dicrotic notch. The decline in pressure during diastole is slight, and hence there is a plateau between each peak. This is especially noticeable in the femoral artery pulse where the pressure at times rises during diastole. Although they serve for comparative purposes of illustration, even these tracings cannot be considered entirely normal since they were taken after a moderately long operative procedure when the vessels were isolated and the hepatic artery divided.

During rapid gastroduodenal artery hemorrhage, there is a striking reduction in the

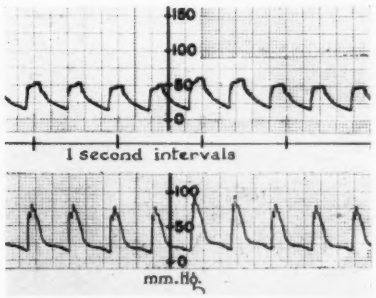

Fig. 2. The alteration in pulse pressure with severe gastroduodenal artery hemorrhage is shown. The hepatic artery peaks are approximately 25 millimeters lower than the femoral. The diastolic plateau of the hepatic artery has disappeared and a dicrotic notch is no longer visible. The pressure of the hepatic artery falls from the systolic peak almost rectilinearly to the next systole.

height of the systolic peak of the hepatic artery pressure as compared to the femoral artery pressure (Fig. 2). The dicrotic notch is no longer visible in the hepatic artery pulse pressure tracing; and, after the systolic peak, the pressure descends almost rectilinearly to the ascending limb of the next systolic ejection. This causes a complete collapse of the diastolic phase in the hepatic artery, but a diastolic plateau is still apparent in the femoral artery tracing. The pulse pressure of the hepatic artery is nevertheless reduced because the systolic peaks are much lower.

The fall in systolic blood pressure and narrowing of the pulse pressure which progresses with gastroduodenal artery bleeding is well demonstrated in Figure 3. At the time when the hepatic artery systolic pressure is 50 millimeters of mercury, the femoral systolic pressure is still 75 millimeters of mercury. As the bleeding continues, the femoral artery systolic pressure tends to sustain itself at 50 millimeters, while the hepatic artery pressure continued to fall.

A similar record obtained during femoral artery bleeding (Fig. 4) shows a uniform decline in both pressures alike. In fact, the hepatic pressure is higher than the femoral pressure. This might be expected since the bleeding occurred from the femoral artery on the side opposite the blood pressure recording. Notice that the hepatic artery pressure recording now shows a dicrotic notch, and that a

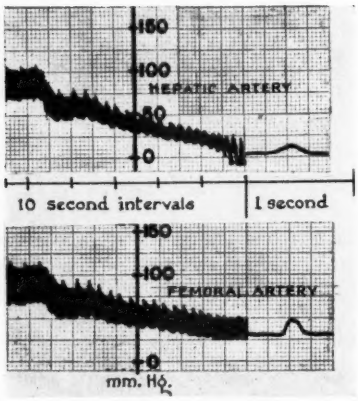

Fig. 3. Blood pressure tracing taken during rapid gastroduodenal artery hemorrhage. The femoral artery pressure below is 75 when the hepatic artery pressure is 50. Thereafter, the femoral artery pressure tends to fall very little at all while the hepatic artery pressure above declines to zero. Notice the absence of dicrotic notch of the pulse pressure on the righthand side of the tracing.

sustained diastolic pressure follows this dicrotic notch.

The blood pressure recordings show an even more striking preferential difference when blood replacement by autotransfusion takes place during the bleeding. Figure 5 shows an increase in blood pressure with a widening of the femoral pulse pressure which takes place when blood replacement is given during gastroduodenal bleeding. The effect on the hepatic artery blood pressure is not as pronounced. Figure 6 shows a reversal of the result with femoral artery bleeding and blood replacement. Here, both are increasing in amplitude equally.

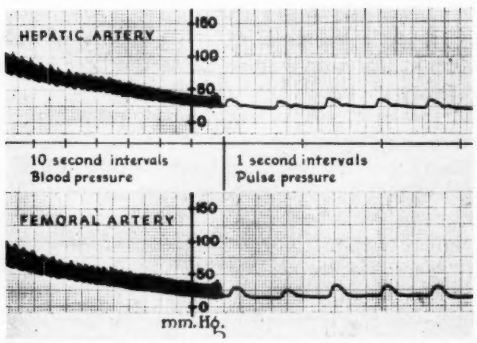

Fig. 4. The blood pressures taken during rapid femoral artery bleeding demonstrate the equality of pressure fall in the hepatic and the femoral artery (contralateral to arterial hemorrhage). The pressure is even slightly higher in the hepatic artery. The dicrotic notch and the diastolic plateau of the hepatic artery persist in the pulse pressure tracing which is on the righthand portion of the tracing.

When blood flow and blood pressures are measured, the differences are even more ostensible. In our experiments, the magnitude of hepatic artery blood flow is far beneath that reported for normal dogs (8). Prolonged anesthesia, hemorrhage, surgical manipulations, and arterial cannulas, all reduce the hepatic artery blood flow and account for the discrepancy. This is not a disadvantage when one considers that patients who have suffered hemorrhage from a peptic ulcer probably have a similar reduction in the hepatic artery blood flow. Figure 7 shows the parallel fall which occurs in femoral and hepatic artery blood pressures with femoral artery bleeding. A profound and selective drop in femoral artery blood flow as compared to hepatic artery blood flow is evident. The recordings in Figure 8 were taken during gastroduodenal artery bleeding. Notice the rapid drop which occurs in the hepatic artery blood flow as compared to femoral artery blood flow. When the hepatic artery blood flow has completely ceased, the femoral artery blood flow is reduced only by $\frac{1}{3}$. Most important is that the hepatic artery blood flow ceases when the hepatic artery blood pressure is about 60 millimeters. At this point the femoral blood pressure is 100 millimeters of mercury. An instantaneous drop in hepatic artery blood pressure and blood flow occurs when gastroduodenal bleeding started. No change is noticeable at this point in the femoral artery blood pressure or blood flow.

When the hepatic artery blood flow had ceased and its blood pressure had fallen as a result of the prolonged gastroduodenal artery hemorrhage, a transfusion was started and the bleeding allowed to continue (Fig. 9). The restoration of femoral artery blood flow and blood pressure is dramatic, but the transfusion effectuates only a trifling alteration in the hepatic artery blood pressure and the hepatic artery blood flow remains nil. When bleeding ceases, hepatic blood flow rises immediately.

DISCUSSION

Wilhelmi and Long have presented evidence to show that the metabolic effects of varying degrees of hemorrhagic shock can be mimicked by hepatic anoxia of varying duration. Complete occlusion of the hepatic circulation for 1 hour or more produces irreversible liver damage. The liver which has been subjected to anoxia becomes unable to form urea from ammonium salts or amino acids, and it loses the power to inactivate the vasodepressor material of Shorr. This vasodepressor material is formed by hypoxic liver tissue both in vivo and in vitro, and contributes to the general peripheral vascular collapse. The experiments of Fine and Seligman demonstrate that hepatic anoxia plays an important role in the initiation and development of hemorrhagic shock in the dog, which can be prevented by cross-circulating the liver with blood from another animal.

Although the liver derives approximately 75 per cent of its blood supply from the portal vein, the portal vein only contributes about 50 per cent of its oxygen supply (3, 8). Normally, the portal vein oxygen tension is 15 volumes per cent (75 per cent saturated) as compared to 19 volumes per cent (95 per cent saturated) for arterial blood. With the generalized reduction of blood flow which occurs with hemorrhage and shock, arterial-venous oxygen differences increase in magnitude since the tissues extract the maximum available oxygen from the sluggishly flowing blood (7, 10). Yet, the arterial oxygen tension remains unchanged (10). Even in early shock, the venous blood flowing from the intestines (portal blood) exhibits a high degree of oxygen unsaturation (about 5 volumes per cent, or 20 per cent saturation); therefore, little is available for the liver from this source (4). Under this circumstance, the liver is completely dependent upon the hepatic artery blood flow for its oxygen supply.

Our data indicate that a striking reduction in hepatic artery blood pressure and especially in hepatic artery blood flow occurs with rapid gastroduodenal bleeding. This reduction is selective as compared to that of peripheral artery blood flow and blood pressure. The experimental results are shown in Figure 8.

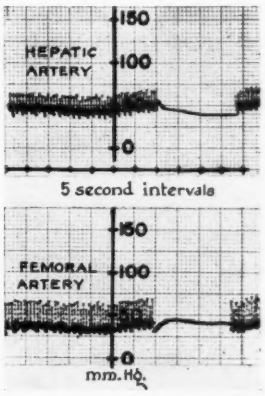

Fig. 5. The blood pressure record taken during femoral artery hemorrhage. The effects of bleeding become more pronounced when a simultaneous autotransfusion is given. Notice that the amplitude of the hepatic pulse pressure is almost as great as is the femoral.

The experimental conditions duplicate the consequences which arise from a massive hemorrhage originating in a peptic ulcer. Since the gastroduodenal artery lies in relation to the first portion of the duodenum, it is in a most vulnerable position (Fig. 10, 1). Erosion into the gastroduodenal artery or one of its major branches would precipitously reduce the hepatic artery blood flow (Fig. 10, 2). Hepatic artery spasm and factors mentioned later further reduce its flow. Because the effects of the anemia of blood loss and the re-

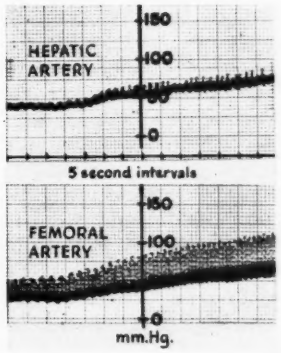

Fig. 6. Blood replacement during persistent gastroduodenal artery hemorrhage primarily restores the femoral artery blood and pulse pressures. The effect on hepatic artery blood and pulse pressures is not striking.

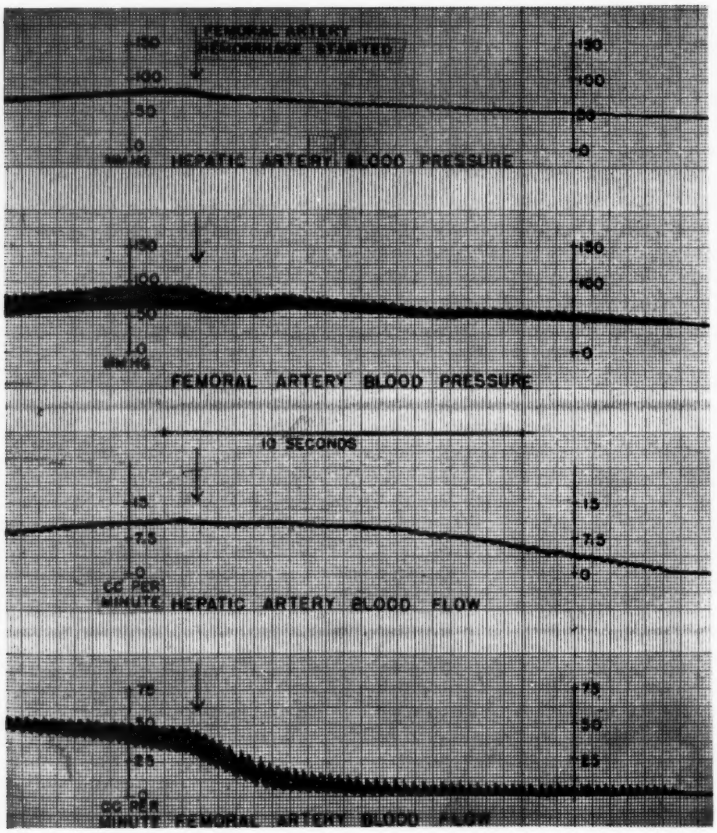
FEMORAL ARTERY HEMORRHAGE STARTED
HEPATIC ARTERY BLOOD PRESSURE
FEMORAL ARTERY BLOOD PRESSURE
10 SECONDS
CC PER MINUTE HEPATIC ARTERY BLOOD FLOW
CC PER MINUTE FEMORAL ARTERY BLOOD FLOW

Fig. 7. Simultaneous records of blood pressure and blood flow were taken during the course of femoral artery hemorrhage. The femoral artery blood flow (lowermost) makes a pronounced decline when compared to the hepatic artery blood flow (second from bottom). It is apparent that the blood pressures do not mimic blood flow.

duced portal oxygen tension are superimposed on this selective reduction in hepatic artery blood flow, hepatic hypoxia becomes progressively more severe (Fig. 10, 3) and eventually produces liver anoxia (Fig. 10, 4). This sequence of events should not be compared to simple occlusion of the hepatic artery which, in itself, is often fatal.

The hemodynamic effects which peripheral artery hemorrhage produce on hepatic artery blood flow and pressure are no different than the effects produced on arterial blood flow elsewhere. A selective reduction in hepatic artery blood flow occurs with gastroduodenal artery hemorrhage because the pressure head at the origin of the hepatic artery is reduced. This reduction in hepatic artery blood pressure is caused by the sudden reduction in peripheral resistance which results from the opening of a large branch of the hepatic artery system (Fig. 10). The reduction in hepatic artery blood flow is most apparent when systemic blood pressure reaches levels beneath 75 millimeters of mercury. One of the deleterious effects on blood flow occurs because of the complete collapse of diastolic pressures leaving the propulsion of blood then dependent solely on short systolic peaks (Fig. 2).

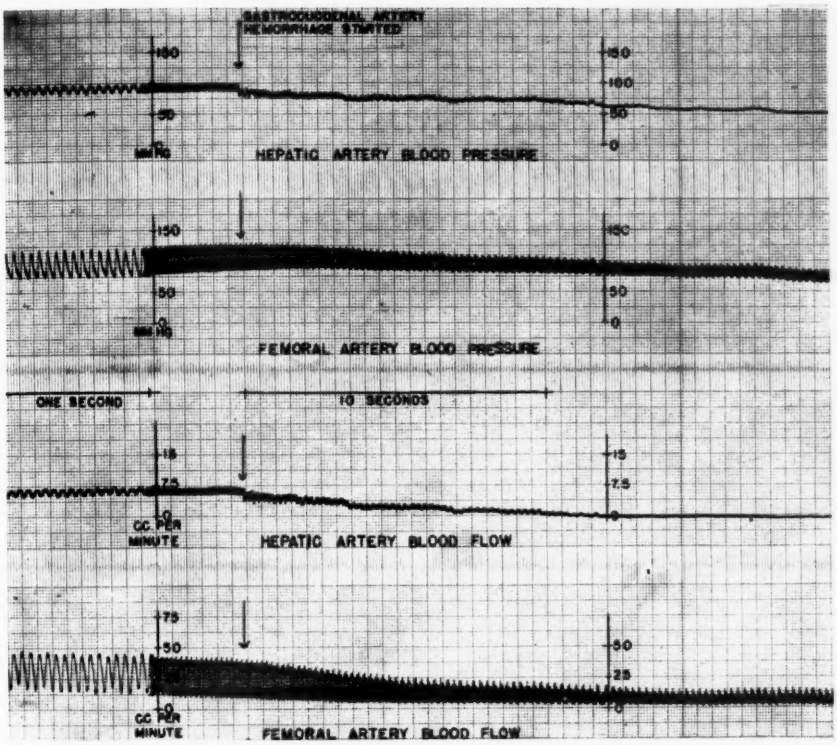

Fig. 8. These simultaneous records of blood flow and blood pressure which were taken during gastroduodenal artery hemorrhage should be contrasted with those in Figure 7. Notice the immediate and selective drop in blood flow which occurs in the hepatic artery (second from bottom). At a time when the hepatic blood flow has ceased, the femoral artery blood flow (bottom) is reduced only by 1/3.

In the case of gastroduodenal artery bleeding, the disproportion between systemic and hepatic artery blood flow reaches its greatest magnitude at low systemic blood pressures. A partial explanation for this fact is that blood seemingly becomes more viscid at low flow rates. With rapid flow rates, the red cells tend to concentrate in the center of the vessel and form an almost solid central core. A central core in effect slides along on a relatively clear layer of plasma. This situation, which obtains at rapid flow rates, is called laminar, axial, or streamlined flow. At low flow rates, axial flow does not occur and each cell goes tumbling along turning on itself and churning up the surrounding blood plasma. Energy is expended producing such eddy currents. The net result is that the resistance to flow is greater at low flow rates; or, in other words, blood seems to be more viscid and more energy is required to circulate it. For these reasons, a rectilinear relationship between blood pressure and rate of blood flow (Poiseuille's law) only occurs at blood pressure levels which are sufficiently high to produce axial flow.

In addition to the hemodynamic factors mentioned which exaggerate the reduction of hepatic blood flow at low blood pressures, the resistance which the liver offers to the flow of blood increases after hemorrhage (15). The hepatic blood flow is further reduced and the hypoxia becomes more severe. According to Blalock, even moderate hemorrhage reduces the portal blood flow by more than half (2).

In the treatment of massively bleeding peptic ulcers, some clinicians willfully pre-

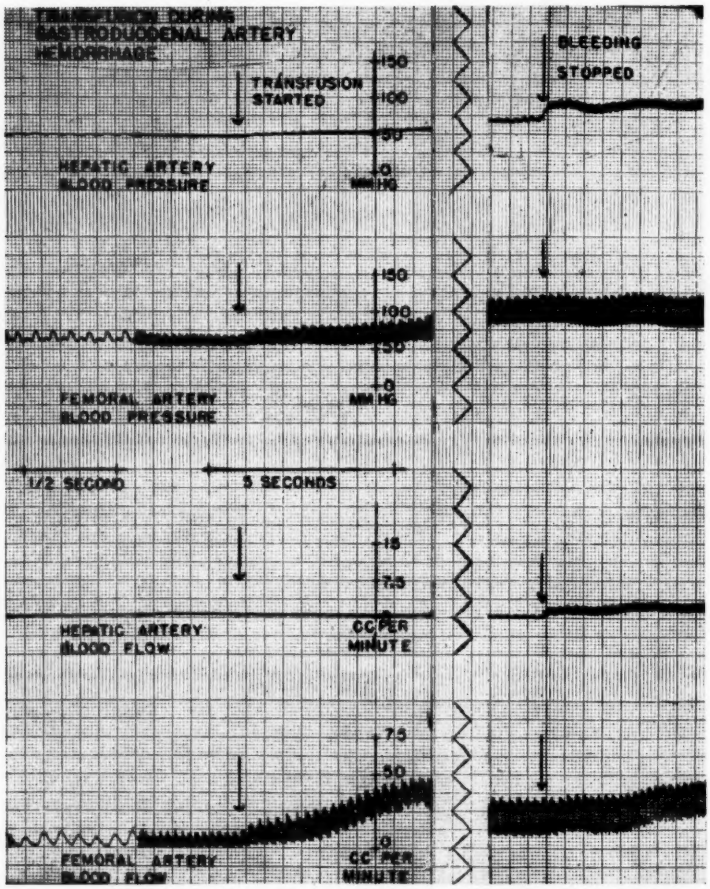

Fig. 9. Recordings were taken during the course of persistent gastroduodenal artery hemorrhage when a rapid autotransfusion was given. The femoral artery blood flow and blood pressure responded with an immediate rise, but the effect on the hepatic artery blood pressure and blood flow is not so apparent. Later, when the bleeding was stopped, an immediate response in hepatic blood flow occurred.

serve the low systemic blood pressures, by withholding transfusion completely or by giving small transfusions slowly. This is advocated to favor clot formation and to prevent any newly formed clot from being dislodged. Our experimental data on gastroduodenal bleeding and gastroduodenal bleeding during blood replacement both indicate that the hepatic artery blood flow is most drastically reduced when the systemic blood pressure reaches low levels; therefore the hepatic anoxia will be most severe at reduced systemic blood pressure levels. To willfully maintain low blood pressures in patients seems contraindicated and is equivalent to the control of hemorrhage by the maintenance of shock. The quantitative replacement of blood loss is necessary to bolster a reduced hepatic artery blood flow (Fig. 6), and to prevent the low portal vein oxygen tensions which occur in shock as well as all of the general effects of reduced blood volume. Urgent surgery should

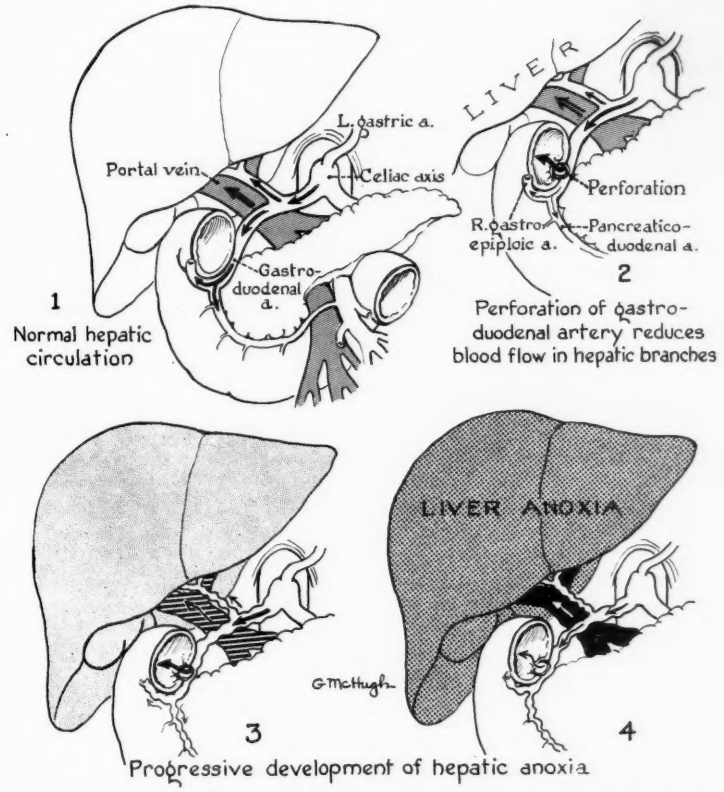

Fig. 10. 1, The blood supply to the liver is illustrated. The rates of blood flow are indicated by the size of the arrows. The degree of oxygen desaturation in the portal vein and in the liver is indicated by the degree of blackness. 2, When an ulcer erodes into the gastroduodenal artery, hemorrhage into the gastrointestinal tract occurs. The blood flow through the hepatic artery is selectively reduced. 3, As the hemorrhage proceeds toward shock levels, there is a decrease in portal vein oxygen tension, and a further reduction in the hepatic artery blood flow. The liver hypoxia is now apparent. Possible spasm of the hepatic artery contributes to the reduction in arterial blood flow. 4, Liver anoxia eventually results from a further reduction in the oxygen saturation of portal vein blood and the almost complete cessation of hepatic arterial flow.

be performed to effect hemostasis as soon as possible. Subtotal gastrectomy with application of gelfoam on the bleeding site would seem to be the procedure of choice.

Because experimental evidence indicates that penicillin therapy aids in protecting the dog against the lethal effects of hepatic anoxia produced by hepatic artery ligation, penicillin and/or other equivalent antibiotics should be administered in all cases of gastroduodenal bleeding (9).

Ravdin has demonstrated the extensive hepatic necrosis which general anesthetic agents produce in the presence of hypoxia. In addition, some anesthetic agents interfere with the in vitro oxygen uptake of tissue slices. An emergency operation in the presence of severe gastroduodenal bleeding is best performed under local, regional, or spinal anesthesia (14), notwithstanding the fact that general anesthesia is advocated by some anesthesiologists (1).

CONCLUSIONS

Although the effects of massive femoral artery bleeding on the limb has long been recognized, the effects of gastroduodenal artery hemorrhage on blood flow of the liver has received little attention. Massive hemorrhage arising from the gastroduodenal artery or a large contiguous branch selectively reduced the hepatic artery blood pressure and blood flow far in excess of that seen in more distal vessels. This selective reduction of blood flow becomes greatest when systemic blood pressure reaches levels beneath 100 millimeters of mercury. In hemorrhage, there is a reduction in the oxygen tension of the portal venous blood which makes oxygen from this source unavailable to the liver. A selective hepatic anoxia results which can be offered as the significant physiological basis for the mechanism of death in peptic ulcer hemorrhage. The deterioration of hepatic function is progressive and with continued anoxia a point of irreversible change is reached. It is therefore logical that urgent surgery be performed to effect hemostasis as soon as possible. The systemic blood pressure must at all times be maintained by vigorous transfusion to support the impaired hepatic oxygen supply.

SUMMARY

Massive arterial bleeding from the stomach or duodenum reduces the blood flow through the hepatic artery selectively. A sequence of events is initiated which produces selective hepatic hypoxia. Hepatic hypoxia has been implicated by several investigators as the fundamental cause of surgical shock. Emergency surgery to bring about hemostasis would be the treatment of choice for this type of bleeding.

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PORTACAVAL SHUNTING FOR PORTAL HYPERTENSION

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PORTAL hypertension the result of obstruction in the portal bed, though rare in incidence, rates deservedly high in clinical importance. Hematemesis, that dreaded omen of serious pathology, claims its victims with deadly regularity. In cases of portal hypertension the incidence of death soon after the onset of attacks of gastrointestinal hemorrhage is exceedingly high, particularly is this true in cirrhosis of the liver. For example, Patek in a follow-up study of 150 carefully treated cases of cirrhosis states that 50 per cent of the patients who had hematemesis were dead of hemorrhage within the 12 month period dating from the onset of their first hemorrhage. Snell reports an even higher mortality; namely, 80 per cent within a year of their first hemorrhage.

THE SYNDROME OF PORTAL BED BLOCK

The syndrome of portal hypertension often referred to as Banti's syndrome is well known; namely, congestive splenomegaly, secondary anemia, leucopenia, thrombocytopenia, and a history of attacks of gastrointestinal bleeding or demonstrable evidence of the presence of esophageal varices.

This syndrome was first described by Banti in 1894 and became known as Banti's disease. It was Banti's concept that the pathologic process originated in the spleen, later to be followed by disease of the liver. This theory led to confusion subsequently when it became obvious that many of the patients did not develop disease of the liver. It is to Dr. Allen Whipple that we owe most for dispelling this confusion. His careful, searching studies of the pathology, natural history, and clinical course of the various obstructive portal venopathies are classic. The facts are that congestive splenomegaly with hypersplenism may be caused by a number of obstructive portal lesions.

Cases of portal hypertension are classified in two groups in accordance with the site of portal block; namely, *intrahepatic*, for example, due to cirrhosis of the liver; or *extrahepatic*, cases in which the liver is normal but portal hypertension results from a block in the portal vein itself or its radicals outside of the liver.

RATIONALE OF PORTACAVAL SHUNTING

Our discussion will be confined to the treatment of portal hypertension by portacaval shunting. The term "portacaval shunt" is used by us to include any type of anastomosis that joins the portal and caval systems of veins.

The veins commonly employed by us are the portal vein anastomosed to the vena cava, and the splenic vein anastomosed, end-to-side, with the left renal vein following splenectomy. In cases of portal hypertension these large veins when anastomosed to the caval system create a direct shunt or circuit having a decreased resistance to blood flow. The shunt is capable of shifting, rapidly, a large volume of blood from the high pressure portal system to the low pressure caval system. This, of necessity, causes a marked fall in portal pressure, as determined by measurement, and immediately relieves the strain upon the overburdened coronary-esophageal circuit of collateral veins, thereby, protecting the patient against the recurrence of hemorrhage.

Of all the surgical procedures that have been employed in the treatment of portal hypertension, the portacaval shunt operation is the one procedure in which the effects upon portal hypertension have been quantitated on the spot by direct portal pressure measurements. The portal pressure is reduced in direct proportion to the size of the shunt and the size of the veins employed in the establishment of the shunt. Furthermore, as a result of routinely measuring portal pressure before

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TABLE I.—RELATIONSHIP OF POSTSHUNT PORTAL PRESSURE TO POSTOPERATIVE CHANGES IN VARICES (ESOPHAGRAM) IN 54 CASES

	Status of varices		
	Disappeared	Diminished	No change
Pressure below 300 mm. H_2O	14	25	4
Pressure over 300 mm. H_2O	1	3	7

and after the establishment of shunts in a considerable number of patients in whom a preoperative and postoperative study of the esophageal varices had been made, the effect of a substantial drop in portal pressure in reducing the size of varices has been observed. And, finally, the follow-up correlation of the subsidence of the esophageal varices with the cessation of hemorrhages postoperatively establishes the rationale of portacaval shunting for portal hypertension.

An analysis of 54 cases of shunting (Table I) shows the relationship of postshunt portal pressure to postoperative changes in esophageal varices. A portal pressure reduction to a level below 300 millimeters of saline occurred following the establishment of shunts in 43 or 80 per cent of the 54 cases. In 11 patients the postshunt portal pressure exceeded 300 millimeters of saline. Of the former group there was disappearance of the esophageal varices in 14 patients; in 25 patients the varices were diminished following shunting and in 4 patients there was no change. Whereas, in the 11 shunted patients in whom the portal pressure exceeded 300 millimeters of saline, the varices disappeared in only 1 patient, became diminished in 3, and remained unchanged in 7 patients. It will be noted that in the group of 43 cases of postshunt pressures below 300 millimeters of saline, there was disappearance or diminution in size of the varices in 39 cases (90 per cent) as against only 4 cases (36 per cent) of the 11 cases of postshunt pressures in excess of 300 millimeters of saline. The shunts or the veins employed in the establishment of the shunts were of inadequate size in these 11 patients who had postshunt pressures in excess of 300 millimeters of saline. On the other hand, shunts of a size adequate to reduce portal pressure below 300 millimeters of saline are generally satisfactory. In our entire series of cases of portal hypertension there have been but 2 patients who gave a history of hematemesis who had portal pressures below 300 millimeters of saline; one had a portal pressure of 280 millimeters of saline and the other of 290 millimeters of saline. The portal vein to vena cava type of portacaval shunt can be counted upon to reduce the portal pressure to a figure well below 300 millimeters of saline. Whereas, there is likely to be a variability in the size of the splenic vein, which is frequently used in the establishment of portacaval shunts, it is regularly of adequate size to reduce the portal pressure to satisfactory levels. Having established the relationship of portacaval shunting with correction of portal hypertension to a reduction in size of esophageal varices, we will now discuss the correlation between a reduction in size or the disappearance of esophageal varices and the cessation of hemorrhage.

In 75 cases of shunting (Table II) preoperative and postoperative esophagram comparisons of varices with relationship to postoperative hemorrhage are made. The relationship is unequivocal; namely, in those cases in which the esophageal varices disappeared or became diminished in size (80 per cent), the incidence of recurrence of hemorrhage was 3 per cent compared to an incidence of 60 per cent in those cases in which the varices remained unchanged.

Finally, a relationship between the recurrence of hemorrhage postoperatively to the patency of shunts has been established as follows: Of 13 follow-up deaths in which hematemeses had occurred postoperatively, at necropsy the shunts were found to be completely closed in 12 patients, and 75 per cent closed in 1 case. This emphasizes the importance of maintained patency of shunts.

In summary, our recorded observations at operation of a marked reduction in portal pressure upon the establishment of portacaval shunts correlated with a reduction in size or disappearance of esophageal varices postoperatively and the cessation of hemorrhage establishes the rationale of portacaval shunting for the treatment of portal hypertension.

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operation of a marked reduction in portal pressure upon the establishment of portacaval shunts correlated with a reduction in size or disappearance of esophageal varices postoperatively and the cessation of hemorrhage establishes the rationale of portacaval shunting for the treatment of portal hypertension.

Having cited proof that the establishment and maintained patency of portacaval shunts, employing either the splenic or portal veins, will prevent the recurrence of gastrointestinal hemorrhage, two important questions arise; namely, (1) Is it technically possible to achieve sustained patency in a high percentage of portacaval shunts? (2) What is the operative risk of the procedure?

THE PROBLEM OF SUSTAINED PATENCY IN PORTACAVAL SHUNTS

Prior to taking up a restudy of portacaval shunting in the early forties, Dr. Allen Whipple and I had to our discredit 1 case each of unsuccessful shunting. These operations (performed in the early thirties) involved anastomotic junction of the mesenteric and spermatic veins in one case and the ileocolic vein to the vena cava in the other. Whereas, we were both duly impressed with the tedium of sewing small, fragile veins deep within the abdomen, I was particularly impressed by the rapidity with which my patient, a cirrhotic in his sixties, died in coma.

In the early 1940's, a decade after our initial failures, we undertook a restudy of the problem of portacaval shunting in the belief that advances had been made that would have an important bearing upon the clinical success of the procedure. The increase in knowledge of cirrhosis of the liver was of particular importance because cirrhosis is the cause of portal hypertension in two thirds of the patients having this malady. The Patek regimen for the treatment of cirrhosis well demonstrated the benefits of a high protein, carbohydrate, and vitamin diet and gave the cue to the preparation of these patients for operations of the magnitude of the shunting procedure. Other advances of great importance were: the availability of blood and plasma through the blood bank for the quick correction of anemia, restoration of proteins and, above all, for the prevention of anoxia and shock due to hemorrhage; improvements in anesthetics and the administration of anesthesia in the prevention of anoxia and shock; absolute control over infection, a must for the success of venous shunts, has been more nearly achieved than ever before in the history of surgery with the coming of the antibiotics; and finally, the potential control of blood clotting with the use of heparin, an important asset in maintaining patency in the smaller venous shunts.

TABLE II.—PREOPERATIVE AND POSTOPERATIVE ESOPHAGRAM COMPARISON OF VARICES IN 75 CASES WITH RELATION TO POSTOPERATIVE HEMATEMESIS

Postoperative status of varices	Intrahepatic No. cases	Extrahepatic No. cases	Total No. cases	Total No. cases of postop. hematemesis
Disappeared	18	8	26	0
Diminished	30	4	34	2
No change	4	11	15	9

Cases of varices disappeared or diminished (80 per cent), with postoperative incidence of hematemesis of 3 per cent.
Cases of varices unchanged (20 per cent), with postoperative incidence of hematemesis of 60 per cent.

In addition to the advances, enumerated, our interest in undertaking a restudy of the problem of portacaval shunting was sparked by the advent of a nonsuture method of blood vessel anastomosis employing vitallium tubes. Dr. Jere Lord and I had employed the method in vein graft bridging of arterial defects in dogs with outstanding success. Likewise, at the time, we had several short term follow-ups in patients whose arterial defects had been successfully bridged. Impressed by the simplicity and time-saving aspects of the method, we adopted its use for the establishment of portacaval shunts. This choice of the nonsuture method over the suture method initially proved to be an unwise choice. It was not easy to detect our error early because many of the shunts remained permanently patent, and those that failed, for the most part, gave evidence of failure many months or in some instances, a year or more after operation. In time necropsy examinations of specimens showing varying degrees of patency of the shunts revealed the mechanism of failure as that of gradual fibrotic occlusion.

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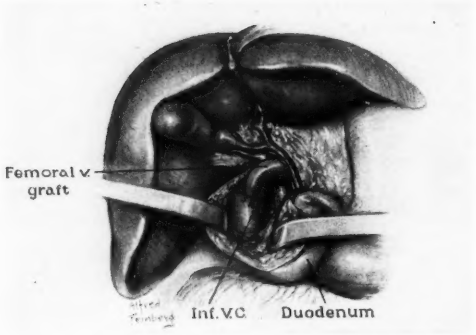

Fig. 1. A drawing to illustrate a completed femoral vein graft anastomosis, connecting a sizable collateral portal vein to the vena cava. Note that the accessory portal collateral vein is well anterior within the hepatoduodenal ligament paralleling the common duct. (Courtesy of *Ann. Surg.*, 1951, 134: 420) (1).

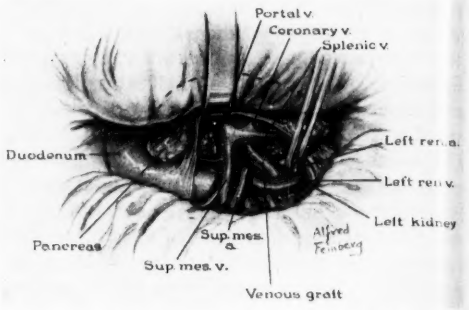

Fig. 2. A drawing to illustrate a completed shunt employing a segment of superficial femoral vein to bridge the distance between the splenic and the left renal veins. Note the coronary vein joining the splenic vein near its junction with the superior mesenteric vein and the large size of the splenic vein in this region. (Courtesy of *Ann. Surg.*, 1951, 134: 420) (1).

This is in contrast to thrombotic occlusion which in our experience is the mechanism of failure of venous shunts employing the suture technique. The practical difference is that the mechanism of failure of suture anastomoses is a rapid one initiated in the immediate postoperative period before intimal covering of the suture line has taken place. This, in our opinion, is adequate reason for the employment of a carefully placed, continuous mattress suture, frequently interrupted and tied to stay sutures, in the performance of these intra-abdominal venous shunts. In growing children interrupted mattress sutures are employed. The effect of the mattress sutures is, of course, to evert the intima when drawn taut and thus bury the silk from contact with the blood. It may as well be stated at this point also, that the best blood vessel technique, in all its detail, is none too good for the success of these relatively low pressure, intra-abdominal, venous shunts. This tendency to early postoperative deposit of thrombus at the suture site no doubt accounts for the considerably higher failure incidence of shunts employing the lesser veins (Table III). Certainly it is with the employment of the smaller veins in the establishment of shunts that an anticoagulant is needed to prevent the initiation of clotting immediately upon opening the shunt at the completion of the anastomosis. It is fortunate indeed that we now have a safe method of continuous, regional heparinization (1) that will insure protection of the anastomosis site against thrombus formation during the immediate postoperative period of healing of the intima. In summary, evidence has accumulated to indicate that if occlusion of a shunt employing the suture technique occurs, it takes place during the early postoperative healing period, unlike the nonsuture method which is likely to become occluded many months after operation as the result of gradual fibrotic occlusion.

TABLE III.—POSTSHUNT BLEEDING IN 40 SHUNTS IN THE EXTRAHEPATIC GROUP, COMPARING VITALLIUM TUBE AND SUTURE TECHNIQUES

Technique	No. of shunts	Postshunt bleeding	
		Minor	Major
Vitallium tube			
Splenorenal	6	2	2
Portacaval			
Small veins	1	—	1
Total	7	2 (28.5%)	3 (42.8%)
Suture			
Splenorenal	20	1	1
Portacaval	1		
Small veins*	12	3	4
Total	33	4 (12.1%)	5 (15.0%)

*These patients were in the postsplenectomy bleeders' group.

Table III indicates the comparative efficiency of the nonsuture and the suture

te niques in the establishment of portacaval sh nts in the prevention of the occurrence of h orrhage in 40 cases of portal hypertension d to extrahepatic portal block. Note the c siderably higher failure percentage em- pl ing the nonsuture vitallium tube tech- ni e compared with the suture technique. T high incidence of postsplenectomy bleed- er mong the suture group made it necessary to mploy lesser veins in the establishment of sh ts. This is because in cases of portal hy rtension secondary to extrahepatic block th portal vein is regularly the site of block, wh h renders it unfit for shunting purposes. Sp nectomy at a previous operation in these 12 ases rendered the splenic vein unfit for di t anastomosis to the left renal vein. This ne ssitated the employment of lesser veins, for example, the mesenterics in this group. Note the failures were 7 in 12 cases.

The recent development of a technique of vein graft bridging between the splenic vein, near its junction with the superior mesenteric vein to the left renal vein employing a segment of femoral vein offers renewed hope for this pathetic group of postsplenectomy bleeders (1). Also in some of the cases of extrahepatic block, a sizable collateral vein may be found paralleling the common duct. We have employed a vein graft to join this vein to the vena cava with the establishment of successful shunts. Figures 1 and 2 illustrate the employment of vein grafts as described. A technique for regional heparinization has been devised (1), employing a fine plastic catheter which is introduced into a small portal radical in close proximity to the shunt. The catheter is secured between two silk ligatures and the other end brought out of the wound and connected for the introduction of a heparin drip immediately after completion of the anastomosis. By employing a constant pressure apparatus, a continuous flow of heparin solution is maintained throughout the postoperative healing period of the anastomosis. A second plastic catheter may be introduced into the vena cava via the femoral vein for blood sampling purposes. The tip of this catheter is advanced up the vena cava to a level just above the level of the shunted portal blood. This permits sampling of shunted portal blood mixed with vena cava blood for the determination of clotting time in comparison with the clotting time of systemic blood drawn from an arm vein. With the continuous administration of a heparin solution via the portal catheter, the systemic blood clotting time may be kept at a safe level of 20 to 25 minutes, and at the same time the vena cava sample, containing shunted portal blood, will range in clotting time between 60 and 75 minutes. Considering the high dilution of the shunted portal blood as sampled from the vena cava the clotting time of the undiluted portal blood passing through the shunt itself must be very high indeed. Finally, at the conclusion of the healing period one can tell positively whether the shunt is patent or not on the basis of differential clotting times done coincidentally on samples of blood taken from the vena cava and the arm veins. Figure 3 is a photograph of a patient showing the two plastic catheters in place. In this patient a shunt was established employing a segment of femoral vein to bridge the distance between the splenic vein, near its junction with the superior mesenteric and the left renal vein.

Fig. 3. Photograph of a patient in whom a femoral vein graft was employed in the establishment of a shunt between the splenic vein near its junction with the superior mesenteric vein and the left renal vein. Note the two exteriorized polyvinyl plastic catheters. The upper catheter is secured between two suture ligatures in the inferior mesenteric vein near its junction with the splenic vein. Through this catheter a continuous heparin-saline drip affords protection against thrombosis of the nearby shunt. The lower catheter is a blood sampling catheter, the tip of which extends up the vena cava to a level above the left renal vein. This enables one to sample shunted blood for clotting times or other purposes.

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TABLE IV.—POSTSHUNT BLEEDING IN 96 SHUNTS IN THE INTRAHEPATIC GROUP, COMPARING VITALLIUM TUBE AND SUTURE TECHNIQUES

Technique	No. of shunts	Postshunt bleeding	
		Minor	Major
Vitallium tube			
Splenorenal	13	2	7
Portacaval	5	—	2
Small veins	—	—	—
Total	18*	2 (11%)	9 (50%)
Suture			
Splenorenal	32	—	4
Portacaval	45	1	2
Small veins	1	—	—
Total	78	1 (1.2%)	6 (7.0%)

*Six patients of this group have been operated upon with a secondary shunt.

In Table IV a comparative summary is made of the nonsuture and the suture techniques in 96 cases of intrahepatic portal block. Note again the high failure rate when the nonsuture technique was employed. Comparing the results of the suture technique in splenorenal shunts with those in which the portal vein was employed reveals less failures with the latter. As a matter of fact, partial (40 per cent) thrombosis of the portal vein was encountered at operation in all 3 failures. In 2 of the failures successful splenorenal shunts have been established. In a recent case of portal vein thrombosis the medial half of the vein was occupied by organized thrombus, and the lateral half contained soft clot. The latter was removed and a side-to-side anastomosis of the portal vein to vena cava was performed. Upon opening the shunt in this patient, the portal pressure fell 220 millimeters of saline to a safe level. Continuous regional heparinization was employed postoperatively with success. We do not employ regional heparinization in an uncomplicated case when employing the portal vein. Due to the higher failure rate of splenorenal shunts, it is now our custom to use regional heparinization for a few days postoperatively, until intimal healing of suture line has taken place.

TABLE V.—POSTSHUNT BLEEDING IN 111 SHUNTS USING SUTURE TECHNIQUE IN COMBINED EXTRAHEPATIC AND INTRAHEPATIC GROUP

	No. of shunts	Postshunt bleeding	
		Minor	Major
Splenorenal	52	1	5
Portacaval	46	1	2
Small veins	13	3	4
Total	111	5 (4.5%)	11 (9.9%)

Table V summarizes the failures when the suture technique was used. If one summarizes the results obtained by using the suture technique for the establishment of shunts, the failure rate in accordance with the size of the veins employed is as follows: portal vein, 6.5 per cent; splenic vein, 11.5 per cent; smaller veins, 55 per cent. These percentages include as failures patients who have had even minor episodes of bleeding postoperatively. It is reasonable to assume that the shunts may still be patent in some of these patients but of inadequate size to shunt sufficient blood to lower the portal pressure to a safe level under all conditions. There is one observation that is outstanding, however, and that is that the use of either the splenic or portal veins in the establishment of shunts is remarkably efficient in the prevention of hemorrhage.

OPERATIVE RISK

Table VI indicates the operative deaths and the causes of death in 166 shunting operations on 160 patients. The figures demonstrate that portacaval shunting may be achieved at minimal risk in patients with extrahepatic portal block having normal livers. The effects of liver damage on operative risk in the intrahepatic group is striking.

In view of the fact that operative risk is of primary concern in the cirrhosis group that make up 63.3 per cent of our portal hypertensive cases, the discussion of operative risk shall be primarily limited to this group.

Table VII shows the correlation of liver function tests with postoperative deaths and follow-up deaths in cases of cirrhosis. A study of this composite table is most informative and the relation of impaired liver function (in terms of liver chemistries) to operative risk and follow-up prognosis is self-evident.

Table VIII presents the mortality rate percentage of the series of cases presented in

TABLE VI.—POSTOPERATIVE DEATHS IN 166 SHUNT OPERATIONS ON 160 PATIENTS

Type of shunt	No. of patients	No. of shunts	Cause of death					Operative deaths No.	Operative mortality per cent
			Operative hemorrhages No. cases	Liver failure No. cases	Thrombosis portal system No. cases	Gastrointestinal hemorrhage No. cases	Inf. myoc.		
Extrahepatic Splenorenal		27	—	—	1	—	—	1	
Portacaval		4	—	—	—	—	—	—	
Others		12	2	—	—	—	—	2	
Total	43	43	2	—	1	—	—	3	6.9
Intrahepatic Splenorenal		54	4	1	3	1	2	11	
Portacaval		65	3	8	—	1 (Sepsis)	1	13	
Others		4	2	1	—	—	—	3	
Total	117	123	9	10	3	2	3	27	21.9
Totals	160	166	11	10	4	2	3	30	18*

*Percentage mortality in 166 shunting operations.

the previous table split according to the averages of the liver chemistries in the postoperative deaths.

Table IX combines the average results of the liver chemistries in the postoperative deaths, the follow-up deaths, and the living cases of cirrhosis of the liver. Noting that the bromsulfalein retention averaged 25.8 per cent in the large group of patients operated upon who are still alive, we have carried the brom-

TABLE VII.—CORRELATION OF LIVER FUNCTION TESTS WITH POSTOPERATIVE DEATHS AND FOLLOW-UP DEATHS

	No. of patients	No. of postoperative deaths	No. of survivals	No. of follow-up deaths	No. still alive	Mortality	
						Postoperative per cent	Follow-up per cent
Serum albumin less than 3 gm. per cent	16	6	10	3	7	37.5	33.3
more than 3 gm. per cent	135	24	111	14	97	17.7	12.6
Ascites* F	32	15	17	7	10	46.8	41.1
R	10	2	8	0	8	20	0
None	117	13	104	11	93	11.1	10.5
Prothrombin time more than 4 sec. above normal	51	13	38	6	32	25.5	15.8
less than 4 sec. above normal	83	15	68	7	61	18	10.3
Cephalin flocculation 3+—4+	44	13	31	7	24	29.5	22.5
1+—2+	104	17	87	10	77	16.3	11.4
Bromsulfalein (30 min. after injection) above 10 per cent	101	24	77	11	66	23.7	14.4
below 10 per cent	37	3	34	3	31	8.1	8.8
Bilirubin above 1 mgm. per cent	46	10	36	6	30	21.7	16.6
below 1 mgm. per cent	91	17	74	10	64	18.6	13.6

*F—indicates cases that failed to respond to medical treatment.
R—indicates cases that responded to medical treatment.

TABLE VIII.—MORTALITY RATE PERCENTAGE OF SERIES CONSIDERED IN TABLE VII, SPLIT ACCORDING TO AVERAGES OF LIVER CHEMISTRIES IN THE POSTOPERATIVE DEATHS

Test		No. of patients	No. of deaths	Mortality rate per cent
Serum albumin	Below 3.58 gm. per cent	34	10	29
	Above 3.58 gm. per cent	117	20	23.4
Prothrombin time above normal	More than 5.5 sec.	30	10	33.3
	Less than 5.5 sec.	104	18	17.3
Bromsulfalein retention after 30 min.	More than 30.3 per cent	31	11	32.2
	Less than 30.3 per cent	107	16	15
Serum bilirubin	Above 1.38 mgm. per cent	32	9	27.9
	Below 1.38 mgm. per cent	105	18	17.1

sulfalein retention analysis in the group of postoperative deaths one step further.

Table X shows the postoperative mortality rates for retentions of bromsulfalein ½ hour after injection in excess of 20 per cent and below 20 per cent. Note the postoperative mortality rate of only 12.3 per cent in 73 patients having bromsulfalein retentions of less than 20 per cent. Comparison of this 12.3 per cent mortality with a postoperative mortality of 6.9 per cent for the 43 patients having extrahepatic portal block, in whom the bromsulfalein retention averaged under 10 per cent, may be taken as evidence that the difference between 10 and 20 per cent bromsulfalein retention indicated a degree of liver damage that was responsible for the 5.4 per cent difference in postoperative mortality. That this evidence is not conclusive, however, is well illustrated by the fact that 64 cirrhosis patients having bromsulfalein retentions averaging 21.1 per cent were operated upon with a postoperative mortality of only 9.3 per cent. This statement indicates that many factors enter into the evaluation of operative risk.

TABLE IX.—AVERAGES OF LIVER CHEMISTRIES IN THE INTRAHEPATIC POSTOPERATIVE DEATHS, FOLLOW-UP DEATHS, AND LIVING PATIENTS

	No. of cases	Prothrombin, time above normal, sec.	Serum albumin gm. per cent	Bromsulfalein retention after 30 min., per cent	Serum bilirubin mgm. per cent
Postoperative deaths	27	5.5	3.58	30.3	1.38
Follow-up deaths	16	4.1	3.69	28.7	1.17
Alive	74	3.6	4.04	25.8	1.10

CLINICAL EVALUATION OF OPERATIVE RISK OF SHUNTING

In the clinical evaluation of operative risk all factors having a bearing on success or failure must be taken into consideration. The factors must be evaluated and correlated in the individual case in arriving at a judgment of whether the patient is a good or poor operative risk for portacaval shunting. In addition to the liver chemistries mentioned in the tables, others, such as serum phosphatase, cholesterol partition, are regularly obtained. In all cases of chronic ascites water balance and electrolyte studies are carried out with, in addition, an evaluation of the patient's response to mercuhydrin.

The importance of a careful history and physical examination cannot be emphasized too much in the evaluation of operative risk. In the first place, the history often gives a cue to the type of cirrhosis present. There are an appreciable number of cirrhotics whom one can classify as poor risks for shunting on the basis of their history and physical examination alone. For example, alcoholics, usually of the older age group, who give a history of anorexia, weakness, and unremitting jaundice who, on examination, are moderately jaundiced, show soft part wasting and the presence of ascites. Such cases would be classed in the poor risk group. This does not necessarily mean, particularly in the younger age group, that a remission of the disease will not take place in some of these patients under the favorable aegis of the modern medical dietary regimen for the treatment of cirrhosis. Unfortunately, however, too often in this group, the gains made in improving their livers is "washed away" by recurring hemorrhage or wasting ascites.

Certain liver chemistry tests may aid in the differentiation of the different types of cirrhosis of the liver, but one must ever keep in mind that a given set of values for these different tests does not have the same significance in the evaluation of operative risk in the different types of cirrhosis. Whereas, we cannot

give a full discussion of this important aspect in the clinical evaluation of operative risk for shunting, outstanding examples may be given:

1. Experience has indicated that deep jaundice, as evidenced by a high serum bilirubin level, does not affect operative risk adversely in cases of cirrhosis secondary to common duct obstruction to nearly the extent that the same level would affect adversely cases of Laennec's cirrhosis.

2. We have gained the impression that the strongly positive (3+ to 4+) cephalin flocculation tests more seriously affect operative risk in Laennec's cirrhosis than in posthepatitis cirrhosis.

3. A moderate elevation of serum phosphatase in cases of Laennec's cirrhosis would seem to affect operative risk more unfavorably than double the value in cases of posthepatitis cirrhosis so affected.

4. Finally, we believe that bromsulfalein retention of a given value affects the operative outcome less in posthepatitis cirrhosis than is the case with Laennec's cirrhosis.

Whereas, there are yet other factors that come up for evaluation in determining operative risk for shunting, the discussion will close with mention of the age factor as follows: There were 6 children with cirrhosis in which the shunting operation was carried out without a postoperative death, but in 3 patients aged 62, 64, and 67 years, there were 2 postoperative deaths, both cardiac.

In Table XI 117 cases of shunting operation in the presence of cirrhosis upon clinical evaluation, are divided into good operative risk and poor operative risk groups, A and B. It is noted that 55 per cent or 64 of the 117 patients were classified as good risk patients. The postoperative mortality in these 64 cases was 9.3 per cent. In group B are classified 53 patients (45 per cent), belonging in the poor operative risk category. The postoperative mortality was 39.9 per cent in this group.

The difference in operative risk between patients having minimal disease of the liver and derangement of function compared with those having extensive disease and impairment of liver function is great indeed. It is comforting to note, however, that portacaval shunting can be accomplished in more than

TABLE X.—CORRELATION OF BROMSULFALEIN RETENTION (20 PER CENT AFTER 30 MINUTES) AND POSTOPERATIVE DEATHS

		No. of patients	No. of P.O. deaths	Mortality rate per cent
Bromsulfalein retention after 30 min.	Above 20 per cent	65	18	27.7
	Below 20 per cent	73	9	12.3

half of all patients having cirrhosis of the liver with a reasonable operative risk (9.3 per cent). Furthermore, taking into account the sizable group having portal hypertension secondary to extrahepatic portal block in whom the liver is normal and the operative risk is low, the over-all picture for portacaval shunting is most encouraging as follows:

Combining the 64 good risk cirrhosis cases with the 43 extrahepatic portal block cases adds up to 107 cases or 66.8 per cent of the entire series of 160 portal hypertensive cases. There were 9 postoperative deaths in this combined group of 107 cases or 8.4 per cent. This indicates that portacaval shunting may be accomplished in at least two-thirds of the cases of portal hypertension at an operative risk well under 10 per cent.

Though we have demonstrated a low operative risk for portacaval shunting (8.4 per cent) in two thirds of all cases having portal hypertension, the question is properly asked what can be done to lower the operative risk of shunting in the remaining one third of portal hypertensive patients who have severely damaged livers?

It is informative to present the average liver chemistry values of the patients classified as good operative risk (group A) for comparison with the average values for group B,

TABLE XI.—POSTOPERATIVE MORTALITY RATE IN 117 PATIENTS WITH INTRAHEPATIC BLOCK DIVIDED INTO 2 GROUPS ACCORDING TO CLINICAL EVALUATION (A, GOOD RISK, AND B, POOR RISK)

	Group A		Group B	
	No.	Per cent	No.	Per cent
Total patients	64	55	53	45
Postoperative deaths	6	9.3	21	39.9

TABLE XII.—AVERAGES OF LIVER CHEMISTRIES IN PATIENTS WITH INTRAHEPATIC BLOCK SPLIT INTO TWO GROUPS (A, GOOD RISK, AND B, POOR RISK) ACCORDING TO CLINICAL EVALUATION

	Group A No. patients	Group B No. patients
Serum albumin (gm. per cent)	4.2	3.4
Ascites F*	5	26
R†	2	6
None	57	21
Prothrombin time above normal (sec.)	3.3	4.7
Cephalin flocculation 3+—4+	19	23
1+—2+	42	30
Bromsulfalein retention after 30 minutes (per cent)	21.1	33.9
Serum bilirubin (mgm. per cent)	0.87	1.5

*F=Failed to respond to medical treatment.
†R=Responded to medical treatment.

poor risk patients. This comparison should have particular significance since the post-operative mortality was 9.3 per cent in the group A, good risk patients, compared to nearly 40 per cent in group B, poor risk patients. Table XII presents the comparison. Note the relatively large number of patients having 3+ and 4+ cephalin flocculation classified in the good risk column: patients for the most part who had posthepatitis cirrhosis. It is informative to note that the average bromsulfalein retention ½ hour after injection is 21.1 per cent in the good operative risk group A cases. Taking this figure into consideration with the figure of 25.8 per cent bromsulfalein retention, average for the 74 living cases of cirrhosis being followed (see Table IX) would seem to indicate that bromsulfalein retentions up to between 20 and 25 per cent have little effect upon operative risk.

We adopted early a relatively broad basis of acceptance of cirrhosis cases for operation *pari passu* with improvement in surgical management as is evidenced by the almost equal numbers of patients in the good risk and poor risk groups. Whereas, such a policy, over the years, obviously cancels out any percentage-wise reflection of improvement in surgical management, there have resulted two substantial groups of shunted cirrhosis cases for comparative analysis and follow-up study.

As would be expected in the poor risk group shown in Table XII approximately half of the patients had intractable ascites in contrast to only 5 of the 64 cases (7.8 per cent) in the good risk group. It is primarily among this group of poor risk cirrhotics having intractable ascites that attempts at surgical intervention are accompanied by considerable risk. On the other hand, it is becoming equally well recognized by the internist that the onset of intractable ascites with repeated paracentesis marks a point of diminishing return from medical management: progressive impairment of liver function is the inevitable result of the vicious circle of chronic protein depletion.

It is an observed fact that portal hypertension can be an important factor in the persistence of ascites in cirrhosis cases and that portacaval shunting will relieve ascites in those treatment failures with unmistakable evidence of portal hypertension.

As further evidence of the importance of portal hypertension as a factor in the persistence of ascites is the fact that intractable ascites can occur in patients having remarkably good liver chemistry values, as for example, the 5 patients listed in Table XII as good operative risk group A cases. It is agreed that in these 5 cases sodium retention was an important co-factor with portal hypertension in the persistence of ascites, yet correction of the portal hypertension by portacaval shunting promptly relieved the ascites.

The natural history of cirrhosis of the liver has taught us to expect a considerable variability of behavior in accordance perhaps with a variability of the degree of initial liver damage, and in certain types of cirrhosis apparently the occasional recurrence of active hepatitis.

Whereas, the modern medical dietary regimen has been of great value in the treatment of cirrhosis, there are patients in whom the pathological process does not appear to be favorably affected over a sustained period. Many such cases as the result of a failing liver develop intractable ascites, primarily the result of altered water metabolism, sodium retention, and serum albumin depletion in spite of thorough treatment. Such patients are end stage cirrhotics and at best have but a few months to live.

Our concern is with that sizable group of cirrhotics who respond to medical management for a time only to develop ascites concurrently with the development of portal hypertension, as evidenced by hemorrhage or the presence of esophageal varices as demonstrated by x-ray examination. It is this group that should be evaluated early for shunting. A good percentage of these patients if referred early for evaluation for shunting will be found to have bromsulfalein retentions ½ hour after injection of under 30 per cent. When put at rest on balanced studies with restriction of sodium to less than 1 gram daily, correction of anemia and repletion of proteins by transfusions and human albumin, if necessary, many of these patients, after 2 or more weeks, will begin to move water, excrete sodium, and stabilize the shift of albumin. It is at this point of progress that one can get a true value of the liver's ability to make albumin in a given case. If the serum albumin stabilizes around 3.3 to 3.5 grams per cent, other liver function values being equally favorable, the risk of shunting is not excessive. Once the shunt is successfully accomplished with the correction of the portal hypertension and the ascites, there is a good likelihood that the patient's liver will again respond under the favorable aegis of modern medical dietary management.

Patients having ascites are grateful for relief and are frequently rehabilitated to usefulness. Our oldest follow-up patient is an ascites patient now 7 years since the establishment of a portacaval shunt. There is a great spread of cases of cirrhosis with intractable ascites correctable by shunting between the average liver chemistry values listed for the good risk group A cases and the poor risk group B cases listed in Table XII. It is our opinion that shunting has a role of increasing

TABLE XIII.—ONE MONTH TO 7 YEAR SURVIVALS IN 130 SHUNTED PATIENTS (40 EXTRAHEPATIC, 90 INTRAHEPATIC)

Survival, years	No. of patients	No. of deaths	No. alive
Extrahepatic 1 mo.—1	6	0	6
1—2	9	0	9
2—3	8	1	7
3—4	5	1	4
4—5	6	0	6
5—6	5	0	5
6—7	1	0	1
Total	40	2 (5%)	38 (95%)
Intrahepatic 1 mo.—1	20	6	14
1—2	23	5	18
2—3	19	3	16
3—4	16	0	16
4—5	9	2	7
5—6	2	0	2
6—7	1	0	1
Total	90	16 (17.7%)	74 (82.2%)

TABLE XIV.—FOLLOW-UP DEATHS IN 130 PATIENTS

Cause of death	Extrahepatic				Intrahepatic				
	Splenorenal	Portacaval	Small veins	Total	Splenorenal	Portacaval	Small veins	Total	Totals
Gastrointestinal hemorrhage	2	—	—	2	3	2	—	5	7
Liver failure	—	—	—	—	—	4	—	4	4
Gastric ulcer	—	—	—	—	2 1 infarc. 1 bleeding	—	—	2	2
Purulent meningitis	—	—	—	—	1	—	—	1	1
Pulmonary embolus	—	—	—	—	1	—	—	1	1
Cerebral hemorrhage	—	—	—	—	1	—	—	1	1
Polycystic kidney (uremia)	—	—	—	—	1	—	—	1	1
Hemocromatosis	—	—	—	—	—	1	—	1	1
Follow-up deaths	2	—	—	2	9	7	—	16	18
Follow-up mortality (per cent)				5				17.7	13.8

importance in this sizable group of cases with ascites complicated by portal hypertension. In going over the case histories of our series of group B cases, we are impressed by the large number of cases in whom unmistakable evidence of severe portal hypertension had existed for a year or more. It is obvious that further liver deterioration had occurred as a result of this delay in many cases. Therefore, we make a strong plea that such cases should be evaluated early for shunting.

Table XIII enumerates the 1 month to 7 year survivals in 130 shunted patients divided in accordance with the site of portal bed block.

Table XIV lists the causes of death in patients who died during follow-up.

SUMMARY

In reporting on 160 cases of portal hypertension in whom portacaval shunts were established, evidence was presented correlating the reduction in portal pressure with reduction in size of esophageal varices and the prevention of hemorrhage.

Factors affecting the maintained patency of shunts were discussed. Either the portal or splenic veins have proved to be of adequate size in the establishment of portacaval shunts regularly to protect patients against the recurrence of hemorrhage. By employing the suture technique, there were but 3 failures in 46 patients (6.5 per cent) when the portal vein was used and 6 out of 52 cases (11.5 per cent) when the splenic vein was used for shunts.

The operative risk of portacaval shunting was discussed in terms of the normalcy of the liver as follows:

In 43 patients having portal hypertension secondary to extrahepatic portal block in whom the livers were normal, there were 3 postoperative deaths (6.9 per cent); whereas, in 117 cases of cirrhosis of the liver the operative mortality was 21.9 per cent. But, classifying the 117 cirrhosis patients into two groups, on the basis of liver chemistry values and clinical factors, in accordance with degree of operative risk, the results were as follows: group A, good risk patients, 64 cases (55 per cent), in whom the operative mortality was 9.3 per cent; group B, poor risk patients, 53 cases (45 per cent), in whom the operative mortality was 39.9 per cent. Combining the 43 good risk patients belonging to the extrahepatic portal block group with the 64 cirrhosis cases classified as good operative risks adds up to 107 cases or 66.8 per cent of the entire series of 160 cases. There were 9 postoperative deaths in the 107 cases, which represents a postoperative mortality rate of 8.4 per cent for two thirds of the entire series.

In the 117 cirrhosis cases averages of the liver chemistries of the 64 good risk group A patients were compared with those of the 53 poor risk group B patients. The incidence of intractable ascites was found to be 8 per cent in the good risk group A cases compared to 50 per cent in the poor risk group B patients.

The evaluation for shunting in patients with ascites having unmistakable evidence of severe portal hypertension was discussed.

Follow-up survivals up to 7 years since operation are 95 per cent for cases of portal hypertension due to extrahepatic portal block and 82 per cent for the intrahepatic block, cirrhosis cases.

CONCLUSION

Evidence has accumulated from analysis of 160 patients having portal hypertension in whom shunts were established that the primary role of portacaval shunting is as follows: (1) to protect patients from untimely death due to hemorrhage; (2) to protect livers in cirrhosis cases from the deleterious effects of recurring hemorrhage and wasting ascites thus affording an opportunity for healing and regeneration of liver parenchyma under the favorable influence of modern medical management.

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THE INFLUENCE OF ANESTHESIA, OPERATION, AND OBSTETRICAL DELIVERY UPON PATIENTS WITH ADRENAL CORTICAL INSUFFICIENCY

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THE serious nature of the clinical syndrome associated with adrenal cortical insufficiency has been recognized since Thomas Addison described this disease in 1855. An acute addisonian crisis, with its associated nausea, vomiting, dehydration, vascular collapse and coma, may end in death despite vigorous therapeutic measures designed to correct the fundamental physiological disorders of this lesion. Clinical crisis may be precipitated even by the slight stress of a mild infection, depressant drugs, and anesthesia and operation.

Vascular collapse may occur during intercurrent disease despite apparently adequate control of water, electrolyte, and carbohydrate metabolism by hormonal and salt replacement therapy. A possible explanation, in part at least, of the vulnerability of the patient with adrenal cortical insufficiency was suggested by Perera who compared certain pharmacodynamic responses in adequately treated patients with Addison's disease and in patients without disease of the adrenals (12). The reactions of these two groups to acetyl-beta-methylcholine were observed. Qualitatively the responses were similar but quantitatively the differences were striking. He suggested that in patients with Addison's disease there is a defect in the response of the autonomic nervous system which may contribute to the inability of the patient to react normally to altered environmental conditions or minor stimuli.

The reluctance to subject these patients to the strain of anesthesia and surgery or labor and delivery has been pronounced. In 1929 Snell and Rowntree maintained that the risk of surgical procedures is prohibitive for the patient with Addison's disease and should not be assumed. In 1933 Greene, Waters, and Rowntree reported 15 cases in which surgery was performed resulting in the death of 11 patients. Of the 4 who survived, operation included drainage of a lumbar abscess, excision of cervical nodes, tonsillectomy, and epididymectomy and orchidectomy. The last patient mentioned was anesthetized with procaine infiltration and represents the first operative survival following such a procedure known to these authors. Included among the procedures causing death are such relatively minor operations as cystostomy, hermorrhoidectomy, orchidectomy, and epididymectomy.

Fitz-Patrick in 1922 reviewed the literature and reported 11 cases of pregnancy in which Addison's disease coexisted. All of these patients died during pregnancy or shortly thereafter. In the case he reported the patient developed an acute crisis but managed to survive. This was the first such survival reported.

In the past two decades with the advent of specific hormone therapy for adrenal cortical insufficiency, a larger number of survivals following operation or pregnancy have been reported in the literature (14, 15, 8, 16). However, even with improved management and understanding of this disease, the operative risk, although considerably diminished, is still a matter for concern (7, 11).

DIAGNOSIS OF ADRENAL CORTICAL INSUFFICIENCY

The adrenal cortex is important in regulating many physiological functions. An important concern to the anesthesiologist and surgeon is its regulation of water and mineral

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metabolism. In the absence of the adrenal cortex there is an immediate and striking increase in the urinary excretion of sodium chloride and water, whereas potassium excretion is decreased. The result is dehydration, hemoconcentration, a decrease in the serum sodium chloride, an increase in serum potassium, weight loss, and hypotension. The reduction in plasma volume and extracellular fluid may be very great (18).

The heart size in these patients is diminished and an abnormal electrocardiogram with prolonged *P-R* and *Q-T* interval, low voltage *QRS*, and low or inverted *T* waves is seen. McGavack measured the heart sizes of a group of patients with adrenal cortical insufficiency and found an average reduction of 16.1 per cent in 3 patients who had Addison's disease without crisis and 31.9 per cent in 5 patients during crisis (9). The blood volumes were restored to normal by the administration of sufficiently large quantities of sodium chloride and water, but the heart volume did not return to normal unless adequate amounts of adrenocortical hormones were also supplied.

Other physiological functions affected are:

Carbohydrate metabolism. This is evidenced by a diminished concentration of glucose in the blood and a greatly reduced glycogen content of liver and muscle. These changes are probably due to a decreased rate of gluconeogenesis. Signs and symptoms of hypoglycemia may appear.

Pigment metabolism. Hyperpigmentation due to increased deposition of normal melanin in the skin and mucous membranes is common.

Lymphoid morphology. Generalized lymphoid hyperplasia and an increase in circulating lymphocytes are frequently seen. Eosinophils may also increase but usually remain in the normal range.

Temperature regulation. This function is impaired. Patients cannot make completely adequate adjustment to either hot or cold environments.

Basal metabolic rate. The basal metabolic rate is reduced to minus 10 to minus 20.

Miscellaneous. Other signs and symptoms include nausea and vomiting, diarrhea, low urinary 17-ketosteroid excretion, an increase in blood nonprotein nitrogen, and radiological evidence of healed or active tuberculosis. Addison's disease should be suspected strongly in patients with tuberculosis of the genitourinary tract.

ANALYSIS OF CASES

Since Addison's disease is relatively rare, the experience of two large institutions was surveyed to obtain records of as many patients subjected to anesthesia and operation as possible. Accordingly, a review of the patients with Addison's disease at the Presbyterian Hospital in New York and the Peter Bent Brigham Hospital in Boston was completed for the last two decades. Both institutions attract a relatively large number of addisonian patients because of the extensive interest in adrenal cortical insufficiency in their respective departments of medicine.

Since 1932 approximately 185 patients with adrenal cortical insufficiency were treated at the Presbyterian Hospital in New York City. Of this number only 11 underwent anesthesia for 14 operative procedures or obstetrical deliveries. Dental extractions or desoxycorticosterone acetate (DCA) pellet implantations were not included in the consideration of surgical procedures. Pertinent details are summarized in Table I.

At the Peter Bent Brigham Hospital in Boston 8 patients received anesthesia for operations over a similar period of time (Table II).

A total of 23 anesthesias were given to 19 different patients for 22 different operations. Three of these patients were operated on twice. One had to be anesthetized two times since marked hypotension developed during the first induction of anesthesia and the operation was postponed for a week. There were 10 males and 9 females ranging in age from 12 to 59 years, with an average age of 36 years. The length of time these patients had known adrenal cortical insufficiency varied from 3 months to 6 years, with an average of 25 months. Five of these patients did not have a diagnosis of Addison's disease prior to operation (Cases 1, 3, 14, 17, and 18A). Of these, 1 patient (Case 3) expired during operation 55 minutes after anesthesia was begun, 2 patients (Cases 1 and 17) died following postoperative circulatory

collapse, and 1 patient (Case 18A) required a postponement of surgical intervention because of uncontrollable hypotension during anesthesia. The fifth case (Case 14) suffered a postoperative collapse but recovered.

Other abnormal findings preoperatively included hypotension, low serum sodium, hypoglycemia, and mild secondary anemia. Six patients had tuberculosis, 1 suffered from pulmonary emphysema, and 1 from hypothyroidism. Two patients came to surgery for a therapeutic interruption of pregnancy; another had 2 normal spontaneous deliveries 30 months apart; and 1 had a cesarean section for a full term pregnancy necessitated by cephalopelvic disproportion.

The specific medication administered as treatment for adrenal cortical insufficiency prior to anesthesia and operation varied. Ten patients were given DCA or adrenal cortical extract, together with sodium chloride, for some time prior to their admission to the hospital or immediately prior to operation or delivery. Four were maintained on DCA or adrenal cortical extract alone, 1 on salt alone, and 1 received adrenocorticotrophic hormone (ACTH) alone. Six patients did not receive any specific medication, of whom 5 were undiagnosed and have been discussed. The specific hormone therapy in Case 19 was unknown. Addison's disease was diagnosed 1 year prior to tonsillectomy.

The preanesthetic medication of most patients did not vary markedly from normal individuals except that the doses were smaller. Eleven patients received morphine sulfate or meperidine (demerol) with scopolamine or atropine; one was given codeine and atropine; 3 received a barbiturate and a belladonna drug; 1 was given seconal alone; 7 received only a belladonna drug. The use of morphine sulfate has been criticized for patients with Addison's disease (2, 18). Of the 5 patients who received this drug preoperatively, 3 expired, but these 3 were unknown addisonian patients at the time of operation and had not been prepared with adrenal cortical derivatives or sodium chloride. One patient who received morphine sulfate had an uneventful recovery, in spite of the fact that she had not had specific hormone preparation.

The anesthetic agents used varied. Ten patients were given ether, 8 cyclopropane, 1 thiopental sodium and nitrous oxide, and 4 were operated upon during local or regional block. The analysis of the physiological changes that occurred during anesthesia or in the postoperative period demonstrates little relationship between the anesthetic agent employed and complications which arose. These data are presented in Tables III and IV.

COMPLICATIONS AND SEQUELAE

Deaths. Three deaths occurred (Cases 1, 3, and 17). These were all in patients anesthetized with ether. However, not 1 of these patients received specific hormone therapy either prior to or during operation.

Hypotension. Hypotension occurred in 14 instances during anesthesia or in the postoperative period. It happened with proportionately the same frequency regardless of the anesthetic agent used. This complication was by far the most frequently seen and may be the result of inadequate specific hormone therapy. Hypotension occurs suddenly and must be treated promptly since it is presumptive evidence of an impending addisonian crisis.

Successful therapy consisted of the administration of large amounts of water soluble whole adrenal cortical extract intravenously and whole blood or plasma in order to maintain an ample supply of cortical hormone throughout the operation and in the postoperative period. A useful clinical index of adequate hormonal treatment is the maintenance of a satisfactory blood pressure.

Fluid retention and pulmonary edema. Overdosage and excessive therapy can occur. Fluid retention, pulmonary edema, and cardiac decompensation may result. This is especially true if DCA and sodium chloride are used in excessively large amounts preoperatively, during anesthesia, and postoperatively. Hypertension alone occurred once during anesthesia with cyclopropane (Case 11B). Since it disappeared postoperatively, the high blood pressure may have been associated with the influence of the anesthetic agent and the management of anesthesia.

In 2 cases (Cases 6 and 8B) fluid retention with evidence of congestive heart failure ap-

TABLE I.—SUMMARY OF PATIENTS WITH ADDISON'S DISEASE ANESTHETIZED AT THE PRESBYTERIAN HOSPITAL, NEW YORK (1932–1950)

Case No.	Sex	Age, years	Duration of Addison's disease	Other diseases	Immediate reason for operation	Preoperative blood pressure	Serum Na mEq./L.	Serum K mEq./L.	Blood urea N mgm. per cent	Blood sugar mgm. per cent	Hb. gm. per cent	RBC	Specific medication before anesthesia
1 SS	M	46	?	Tbc. of kidney, chronic pulm. tbc.	Tbc.-testis, epididymis	106/52			75	100	12.2	4.8	None
2 MD	M	26	3 mo.	None	Fistula in ano	96/60	133.2	4.4		88	13.6	4.8	DCA NaCl
3 RH	F	35	?	Chronic pulm. tbc.	Red degeneration of fibroids, rupture of cystic ovary	90/60			41	55	11.1	4.2	None
4 DW	F	12	18 mo.	None	Abscess of thigh	98/70	127.4		29	69	15.1	4.4	DCA NaCl
5 HR (A)	F	36	10 mo.	Term pregnancy	Cephalopelvic disproportion; hemorrhage from wound	150/90	136				10.0	3.2	DCA NaCl Lipoextract
(B)		36	10 mo.		Hemorrhage from wound	150/90	136				12.8	4.6	Lipoextract
6 MS	F	31	3 yr.	None	3½ mo. pregnant	85/50	134.3		9	85	13.0	4.0	DCA NaCl Lipoextract
7 EG	F	32	6 yr.	None	2 mo. pregnant	102/64	135.8		8	56	12.0	3.9	Percorten
8 SR (A)	F	25	19 mos.	None	Term pregnancy	110/70	134.3	4.0			13.0	3.8	DCA, lipoextract, percorten NaCl
(B)		28	4 yr.	None	Term pregnancy	110/70	133.5	4.4		62	11.0	3.6	DCA, NaCl, lipoextract
9 WS	M	28	1 yr.	Pulm. tbc.	Appendicitis	112/70	133			85	14.7		DCA, NaCl, lipoextract
10 EP	F	39	3 mo.	Frequent upper respiratory infection	Need for submucous resection	100/60	123				12.8	4.5	None
11 BN (A)	M	43	6 mo.	Tbc.	Pyelitis	110/70	137	5.0	13		11.0	3.7	NaCl
(B)		44	15 mo.	Tbc.	Sinus tract flank	120/70	142.9	4.3		83	12.2	4.2	DCA, NaCl

peared postoperatively and cleared when the dosage of DCA was diminished or administration completely stopped for a few days. Both of these cases received large doses of DCA, lipoextract, and sodium chloride preoperatively. These medications were continued into the immediate postoperative period.

Case 6 developed edema of the legs 30 hours after operation. The salt was discontinued and the dose of DCA diminished. Since her serum potassium was found to be low (2.3 milliequivalents per liter), 1.5 grams of potassium salt was added to the diet on the following day. These measures resulted in ab-

TABLE I.—SUMMARY OF PATIENTS WITH ADDISON'S DISEASE ANESTHETIZED AT THE PRESBYTERIAN HOSPITAL, NEW YORK (1932–1950)—Continued

Date of oper.	Premedication	Operation	Type of anesthesia	Time of anesthesia	Changes during anesthesia	Medication during anesthesia	Postoperative results
2–27–33	M.S., 15 mgm. Atrop., 0.4 mgm.	Orchidectomy, epididymectomy	GOE	27 min.	None	None	Next day: weakness, disorientation; hypotension; (B.P. 70/40) died 2 wks. later in Addisonian crisis
5–17–39	Cod., 60 mgm. Scop., 0.6 mgm.	Excision fistulo in ano	GOE	50 min.	None	None	Uneventful recovery
10–14–40	M.S., 12 mgm. Atrop., 0.4 mgm.	Supracervical hysterectomy	GOE	55 min.	Expired 55 min. after anesthesia begun	Saline 500 c.c.	Died on operating table
10–5–41	Scop., 0.3 mgm.	I & D of thigh abscess	Ether OD	7 min.	None	5% dextrose in saline	Hypotension (BP 52/40) successfully treated by shock position
6–8–46	Scop., 0.3 mgm.	Cesarean section	Cyclopropane	55 min.	None	Blood 500 c.c.	B.P. Stable. Developed bleeding from wound. Treated with 500 c.c.of blood
6–9–46	Demerol, 50 mgm. Scop., 0.3 mgm.	Hemostasis, closure of wound	Cyclopropane	25 min.	None	None	Wound explored 1st day postoperatively. Fever for 10 days (endometriosis)
2–6–47	Demerol, 50 mgm. Scop., 0.6 mgm.	Supracervical hysterectomy	Cyclopropane	60 min.	Hypotension, BP, 75/50	Blood, 1000 c.c. 5% dextrose in saline, 800 c.c.	Complete recovery Leg edema due to excessive adrenocortical hormone therapy. Stopped salt, cut down DCA, stabilized in 2 days
2–17–47	Demerol, 50 mgm. Scop., 0.5 mgm.	D & C	Cyclopropane	30 min.	Hypotension, BP, 96/79	Blood, 500 c.c.	Hypothermia; temperature of 96°; hypotensive-BP, 82/48; successfully treated with intravenous fluids
6–2–47	None	Vaginal delivery with episiotomy	Cyclopropane	38 min.	None	Scop., .4 mgm. Blood, 500 c.c.	Uneventful recovery
12–2–49	Demerol, 50 mgm. Scop., 0.3 mgm.	Vaginal delivery with episiotomy	Cyclopropane	45 min.	None	Blood, 500 c.c.	Pulm. congestion, cardiac enlargement, edema peripherally for 5 days due to excessive ACH therapy; receded when extracts discontinued
9–23–49	Demerol, 50 mgm. Scop., 0.3 mgm.	Appendectomy	Paravertebral block procaine pontocaine	48 min.	None	Blood, 500 c.c.	Uneventful recovery
1–30–50	M.S., 9 mgm. Scop., 0.4 mgm.	Submucous resection	Pentothal, N_2O-O_2	50 min.	None	None	Uneventful recovery; begun on DOCA and NaCl
1–16–50	M.S., 12 mgm. Scop., 0.4 mgm.	Nephrectomy	Cyclopropane	2½ hrs.	Hypotension, BP, 80/50	Blood, 500 c.c.	Hypotension (BP, 76/60); successfully treated with lipoextract, blood and 5% dextrose in saline i.v.
11–3–50	Demerol, 75 mgm. Scop., 0.4 mgm.	Excision sinus tract flank	Cyclopropane	75 min.	Hypertension, BP, 150/100	5% dextrose in water, 150 c.c.	Uneventful recovery

sorption of the edema in 48 hours. Case 8B exhibited pulmonary congestion, cardiac enlargement, and peripheral edema postoperatively which lasted 5 days and receded only when all adrenal cortical hormone therapy was stopped.

Goodof and MacBryde reported that hearts of patients with Addison's disease are small and exhibit brown atrophy. They have a poor reserve and there is electrocardiographic evidence of myocardial damage in a large percentage of the cases. In crisis large amounts of sodium chloride, water, and DCA are given. The volume of blood plasma is increased because of the retention of sodium chloride. The sudden addition of a greatly increased load

TABLE II.—SUMMARY OF PATIENTS WITH ADDISON'S DISEASE ANESTHETIZED AT THE PETER BENT BRIGHAM HOSPITAL, BOSTON (1944–1950)

No.	Sex	Age years	Duration of Addison's disease	Other diseases	Immediate reason for operation	Preoperative blood pressure	Serum Na mEq./L.	Serum K mEq./L.	Urea N mgm. per cent	Blood sugar mgm. per cent	Hb. gm. per cent	RBC	Specific medication before anesthesia
12 HJ	M	59	1 yr.	Pulm. tbc.	Renal tbc.	160/110			10	87	15.8	5.1	Eschatin
13 DS	M	52	5 yr.	None	Appendicitis	108/74			7	76	8.4		Percorten, eschatin, plasma
14 EC	M	12	?	None	? Cerebellar tumor	100/65			20	47	13.7		None
15 JP	M	28		Pulm. tbc.	Appendicitis	105/65			6	118	14.8		Eschatin, NaCl
16 MN	F	49	6 yr.	Hypothyroidism	Sclerosing hemangioma arm	104/62	136	5.3	21	81	15.0		DOCA, comp. E (thyroid)
17 FT	M	55	?	Pulm. emphysema	Adenoca. rectum	114/84			11		13.8		None
18 MB (A)	F	47	?	None	Pituitary tumor	185/120			14		12.0		None
(B)						160/80			10	212 (PO)	10.3	3.3	ACTH
19 EM	M	?	1 yr.	None	Tonsillitis	?							?

may cause circulatory failure and death. Much potassium is also excreted and the serum potassium becomes low. This ion is necessary for the normal functioning of the heart. In a patient who died in failure, the postmortem findings in the cardiac muscle were similar to those seen in potassium deficiency. They, therefore, suggest use of normal amounts of potassium (4 to 5 grams per day) while the patient is under specific therapy for adrenal cortical insufficiency. McGavack also advocates replacement of potassium (10).

Currens and White found that electrocardiographic changes in patients who suffered congestive heart failure from excessive DCA therapy were similar to the changes associated with low serum potassium. The congestion occurred without hypertension and responded well to digitalization. They suggested the use of digitalis for the control or prevention of congestive failure. Added potassium to the diets of patients receiving large amounts of DCA was also advocated. To determine whether DCA is used in excessive dosage, serial electrocardiograms become important in following the patient.

Perera, Knowlton, Lowell, and Loeb studied the effects of DCA and sodium chloride on the blood pressure and blood volume in patients with Addison's disease (13). Salt alone over a period of months did not cause any hypertension. The plasma and total blood volumes remained normal. In those patients who were given DCA over a period of 1 to 2 years, hypertension frequently appeared. The blood pressure levels bore no relationship to the minimal peripheral edema seen. The ion, plasma, and total blood volume were normal and there were no cardiovascular signs of failure. They suggested that DCA probably acts to constrict the peripheral vascular system directly or indirectly. In contrast to this, rapid cardiac dilatation and failure may develop from excessive DCA and salt in the treatment of crisis. In this group no hypertension appears.

TABLE II.—SUMMARY OF PATIENTS WITH ADDISON'S DISEASE ANESTHETIZED AT THE PETER BENT BRIGHAM HOSPITAL, BOSTON (1944–1950)—Continued

Date of oper.	Premedication	Operation	Type of anesthesia	Time of anesthesia	Changes during anesthesia	Medication during anesthesia	Postoperative results
3-7-44	Phenobarb., 100 mgm. Atrop., 0.6 mgm.	Nephrectomy	Ether OD	105 min.	Hypotension	Plasma, 50 c.c. Eschatin, 5% dex. saline 1500 c.c.	Uneventful recovery
11-28-44	None	Appendectomy	Local procaine	70 min.	Hypotension BP 82/64	Eschatin, plasma, 325 c.c. 50% dextrose 50 c.c.	Uneventful recovery
9-30-46	Atrop., 0.3 mgm.	Bilat. burr holes	Avertin ether	105 min.	None	None	Marked hypotension; treated successfully with percorten
4-21-48	Seconal, 100 mgm.	Appendectomy	Cont. spinal, procaine	60 min.	Hypotension	Eschatin, albumin	Uneventful recovery
5-10-48	None	Excision hemangioma arm	Local procaine	?	None	None	Uneventful recovery
12-2-48	M.S., 10 mgm. Atrop., 0.4 mgm.	Resection of rectosigmoid	Pent. ether	4 hr. 25 min.	Hypotension BP 70/50	Blood, 1000 c.c. 5% dext./water 2000 c.c.	Treated with eschatin; neosynephrin; fluid intravenously; died 3rd postop. day
12-7-48 OP.	Nembutal, 100 mgm. Atrop., 0.4 mgm.	Postponed hypotension	Pent. ether	90 min.	Hypotension BP 70/50	Blood, 500 c.c. 5% dext./water 1000 c.c. Eschatin	Hypotension successfully treated with blood; ACTH, operated 1 week later
12-13-48	Atrop., 0.4 mgm.	Frontal craniotomy partial removal pituit. tumor	Pent. ether	4 hr. 40 min.	Hypotension BP 90/50	Blood, 1000 c.c., eschatin, ACTH 5% dext./water 1300 c.c.	Uneventful recovery
11-16-50	Nembutal, 100 mgm. Atrop., 0.4 mgm.	Tonsillectomy	Ether	?	?	?	Uneventful recovery

COMMENTS AND CONCLUSIONS

A group of 19 patients with adrenal cortical insufficiency who were anesthetized 23 times for operation or obstetrical delivery has been presented. An effort was made to determine if any specific anesthetic agent or method offered any advantages or disadvantages in Addison's disease. It must be borne in mind that this is a relatively rare condition and that clinical experience in anesthesia for these patients has been infrequent. The number of cases presented is small so that any generalizations can be made only with difficulty and with reservations.

Most of the patients were anesthetized with cyclopropane (8 cases) or ether (10 cases). A small number received regional or local blocks (4 cases), and 1 was given thiopental intravenously with nitrous oxide. Yet, proportionately, complications occurred as frequently in all groups. No one drug or method was without harmful effect. It seems that anesthetic management as a whole is largely a matter of doing the least harm rather than the most good. These patients respond to the stress of operation and anesthesia over a narrow range of compensation. Premedication should be minimal in dosage and with as few drugs as possible. Absolute precision in technique to avoid anoxia, asphyxia, or hypotension is mandatory. Agents or techniques which repeatedly produce significant falls in arterial pressure are inadvisable. These include spinal anesthesia, avertin, and profound depths of inhalation anesthesia. An alert watch for hemorrhage and excessive trauma must be kept because circulatory collapse is apt to be sudden and more severe than in normal patients. However, prior to 1930 and the advent of adrenal cortical preparations for the therapy of Addison's disease, it was most unusual for any of these patients to survive operation or obstetrical delivery. The condition of the 3 patients who died in the group presented here were all undiagnosed and they received no specific adrenal cortical preparation before

TABLE III.—CLINICAL COURSE DURING ANESTHESIA

Anesthesia	Total No. patients	No. cases uneventful	No. cases hypotension	No. cases hypertension	No. deaths
Cyclopropane	8	4	3	1	0
Ether	10	4	5	0	1
Block	4	2	2	0	0
Pentothal	1	1	0	0	0
Total No.	23	11	10	1	1

TABLE IV.—CLINICAL COURSE AFTER ANESTHESIA AND OPERATION*

Anesthesia	Total No. patients	No. cases uneventful	No. cases hypotension	No. cases edema	No. deaths
Cyclopropane	8	4	2	2	0
Ether	8	4	2	0	2
Block	4	4	0	0	0
Pentothal	1	1	0	0	0
Total No.	21	13	4	2	2

*Only 21 cases are tabulated here. The 2 cases not considered were: (1) Case 3 who died during operation and (2) Case 18A in which operation was postponed following uncontrollable hypotension during induction of anesthesia.

their operations. The significant difference in the survival of anesthesia and operation by a patient with adrenal cortical insufficiency today depends on good medical preparation and intelligent replacement therapy with adrenal cortical extracts, sodium chloride, dextrose, and water to bring a diminished circulating blood volume back to normal and combat dehydration and hypoglycemia. During operation and anesthesia, the need for adrenal cortical hormone by the body appears to be increased. If any evidence of circulatory collapse appears, immediate therapy with intravenous aqueous extracts, plasma, or whole blood is life saving. Postoperatively, the demand for hormone is still high and careful watch for the signs of crisis is imperative.

It can be suggested, with reasonable certainty, that surgical operation during well managed anesthesia may be undertaken with greater freedom than was hitherto considered possible if hormonal and salt replacement is conducted intelligently.

CASE REPORTS

The courses of 2 patients with adrenal cortical insufficiency who were anesthetized and operated upon are presented below. Both are very young children and were not included in the groups already discussed.

CASE 1. L.Y., male, aged 2½ years. The patient was admitted for tonsillectomy following frequent bouts of tonsillitis and upper respiratory infections. He had been suffering from adrenal cortical insufficiency since 2½ months of age. Treatment consisted of 12.5 milligrams of cortisone and 5 grams of sodium chloride daily. On admission the serum sodium and potassium were 117 and 6.5 milliequivalents per liter respectively. Blood pressure was 80/60.

Following admission, cortisone was increased to 25 milligrams per day, salt to 8 grams per day, and aqueous adrenal cortical extract injected intramuscularly in doses of 6 milliliters twice a day. After 1 week of this regimen, the serum sodium rose to 132 milliequivalents per liter and serum potassium was 6.0 milliequivalents per liter. Operation was decided upon for the following day.

Preoperatively the patient was given 200 milliliters of 5 per cent dextrose in water intravenously followed by normal saline which was running when the patient reached the operating room. Premedication consisted of meperidine (demerol) 10 milligrams and scopolamine 0.15 milligram intramuscularly at 6:00 a.m. Anesthesia was begun at 7:10 a.m. At this time the blood pressure was 110/80 and the pulse 130. A smooth induction was performed with cyclopropane. Anesthesia was continued with open-drop ether and deepened to plane 2 of the third stage. At 7:45 a.m., just before the operation was begun, ether was insufflated into the patient's pharynx. Following adenoidectomy, the patient developed slight laryngospasm. The anesthesia was deepened and tonsillectomy performed without further complications. Operation and anesthesia ended at 8:20 a.m. During laryngospasm the blood pressure rose to 140/100. At the end of operation it was 110/80 and the pulse 110.

There were no significant changes in the vital signs postoperatively. The patient received 325 milliliters of normal saline intravenously during operation and immediately afterward. The adrenal cortical extract was discontinued 3 days later. The patient was discharged on the fourth postoperative day, in good condition, on a maintenance dose of cortisone 25 milligrams and sodium chloride 6 grams per day by mouth. On the day of discharge serum sodium was 140 milliequivalents per liter and serum potassium 5.8 milliequivalents per liter.

CASE 2. S.B., aged 2 years. This patient was a pseudohermaphrodite admitted on August 1, 1950 for laparotomy for the correct diagnosis of sex. "She" had been suffering from adrenal cortical insufficiency since the age of 2½ months. This was controlled with DCA and sodium chloride. The dosage of these drugs had been gradually reduced so that at the age

of 1 year the DCA and salt were completely eliminated and the patient remained well.

No specific preparation with regard to the adrenal insufficiency was carried out preoperatively. On August 4, 1950 cystoscopy was performed during vinethene-ether anesthesia. The patient had been premedicated with seconal, 45 milligrams, and scopolamine, 0.2 milligram. The procedure, of 25 minutes' duration, and the postoperative course were uneventful.

On August 8, 1950 a laparotomy was performed. The premedication was the same as for cystoscopy. Induction was performed with cyclopropane followed by open-drop ether. No fluids were given during the operation which lasted 30 minutes. A few hours postoperatively the patient suddenly became semicomatose and developed complete peripheral circulatory collapse. Therapy, for the addisonian crisis, consisted of 3 milliliters of lipoadrenal extract intramuscularly, a clysis of 150 milliliters of M/6 sodium lactate and 150 milliliters of 5 per cent dextrose in water. A cut down was performed and 20 milliliters of aqueous adrenal cortical extract given intravenously followed by 250 milliliters of 5 per cent dextrose in normal saline and 150 milliliters of plasma, with improvement. Intravenous fluid therapy was continued for 2 days. To the specific therapy of lipoextract 2 milliliters per day, DCA 2.5 milligrams and sodium chloride 5 grams per day were added on the second day. Three 150 milliliter whole blood transfusions were given on the third, fourth, and fifth day postoperatively. The patient improved continuously and was discharged in good condition on the fifteenth postoperative day receiving 2.5 milligrams DCA and 5 grams salt daily.

These 2 cases demonstrate the sharply contrasting postoperative results which may be obtained in patients with adrenal cortical insufficiency. Proper preoperative hormonal and electrolyte preparation is absolutely essential.

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NONOPERATIVE TREATMENT OF PERFORATED PEPTIC ULCER

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RECENT reports in the literature have suggested the safety of nonoperative treatment in ruptured peptic ulcer. These reports have been uniformly enthusiastic. Those from England (2, 4, 5, 9, 11) suggest that a new era in the treatment of this condition has been reached. Others, including those from this country (1, 3, 8, 10), warn against the general acceptance of such "conservative" therapy but in the same breath report results seldom equaled by operative means. They vary from zero mortality (8) in a consecutive series of 34 patients to 10 or 15 per cent in smaller groups (9, 11). The mortality for approximately 100 reported cases (including this series) has been about 5 per cent.

Certainly many will seek to duplicate these excellent results. None can deny that there is some merit in nonoperative treatment of ruptured peptic ulcer, but just how far the trend should be carried is still an open question.

The reports mentioned are to some extent misleading. They imply a safety not inherent in the treatment. In order to amplify this opinion, our own experience with this method should be discussed. Qualification for such evaluation stems from study of a series of cases treated without operation during the last 15 years. The number of patients so treated is not great, but time has allowed the formulation of certain concepts which should be presented.

The premise on which nonoperative therapy is based is that a perforation in the duodenum or stomach will seal off if the stomach is kept entirely empty. In fact, it frequently seals off with the stomach still full. We have all experienced the necessity of actually having to separate recent fibrinous adhesions in order to reach the site of perforation. Certainly nature has thus sealed off more than half of peptic ulcer perforations by the time the surgeon attempts to make a repair.

The most important feature of nonoperative care is maintaining a completely empty stomach. This is accomplished by a nasal gastric suction tube. Should this tube become obstructed the gastric contents under pressure might again gush through the sealed off ulcer rent. It is obvious that continued suction and patency of the gastric tube are all important.

SERIES NOT TREATED BY OPERATION

Interest at the Indianapolis General Hospital in nonoperation of ruptured peptic ulcer started some 15 years ago. At that time 2 patients with perforated ulcer were admitted in an almost moribund state. Perforation had occurred more than 12 hours before. Immediate operation seemed out of the question. The patients received intravenous fluids and gastric suction was started. To this they responded excellently and at the end of several hours were completely out of shock. Examination of their abdomens indicated rigidity in only the upper portion. A course of watchful waiting was therefore pursued and both patients continued to an uneventful convalescence.

This recovery without operation was completely foreign to any of our surgical concepts up to that time. Nevertheless, it seemed to be a logical method of attack for those ulcers which had already become sealed off. In order to determine in which cases the ulcer had been closed by adhesions and in which the perforations were still patent, it was decided to explore the possibilities of a nonoperative approach in an occasional favorable case. However, it was by no means certain which cases might prove favorable.

About this time Wangensteen reported a similar experience with 3 patients. One of these was lost after 2 weeks but the other 2

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survived. A few years later Ravdin and Johnston reported success with 3 others. No subsequent communications were made by these authors and it was assumed they believed the method was not without fault.

We have continued to treat an occasional patient without operation. There have been 24 such cases at the Indianapolis General Hospital and the Indianapolis Veterans Hospital. These did not include all the cases which were thought suitable. Nevertheless, all treated in this manner were suitable according to our criteria. In all 24 patients it was possible to make a choice as to which type of treatment should be carried out. No moribund patients whose condition precluded any thought of operation were included nor any with questionable diagnostic problems which might delay and confuse therapy.

During this same period there were 220 other patients with peptic ulcer admitted to these same hospitals who were treated by immediate surgery. The results obtained in this group need not enter into our present discussion. The size of the group merely indicates a fairly active ulcer service.

In 20 of the 24 cases treated without operation perforations were proved by x-ray demonstration of gas beneath the diaphragm or by definitive operation a few weeks later. Four cases are included because their history and course were so typical as to leave no question in our minds that a perforation had occurred. A single x-ray examination in these did not demonstrate subdiaphragmatic gas.

It must be emphasized that in all 24 cases a choice could be made as to operation; the patient was not too sick and the diagnosis was clear. They were treated as suggested with continuous gastric suction and according to the method described so well by Bertram.

The patients of this series ranged in age from 28 to 80 years. They were first seen at the hospital from 1 hour to 72 hours after perforation. Only half were seen less than 12 hours after onset.

Nonoperative treatment was chosen because the perforation was thought to be sealed off and physical signs were largely limited to the upper abdomen. It is fully admitted that physical signs may be misleading and that occasionally the sealing off might not have taken place. Acute gall bladder disease or appendicitis occasionally mimic perforated peptic ulcer. It would seem that this failure to be sure of what has occurred inside the abdominal cavity is the chief drawback to watchful waiting.

There were 2 deaths in the group (8.3 per cent). One of these was in an 80 year old man who died 28 days after admission with subphrenic abscess and empyema. The other was in a 51 year old man with a 4 day old perforation on admission. This was watched for 2 days. Operation at that time demonstrated a large walled-off abscess filled with air and duodenal contents. This communicated freely with a huge (3 cm.) perforation in the duodenum which would never have closed spontaneously. The perforation was sutured but the patient died 36 hours later. It should be pointed out that both these patients might still have died from their respective complications even if they had been subjected to immediate operation.

We are definitely of the opinion from a study of our own cases and those in the literature that the complication of subphrenic abscess is somewhat higher in patients without operation. In approximately 100 cases of perforated ulcer not operated upon which are now reported in the literature (including this series), the complication of subdiaphragmatic abscess occurred 9 times.

As a rule our patients recovered promptly. The gastric suction could usually be discontinued on the fourth day and often on the third. A Sippy or modified soft diet was usually well tolerated by the end of the first week. The hospital stay was somewhat prolonged over patients treated with operation. (Perhaps this was partially to convince ourselves that all was well.) So far, 4 of our patients have had gastric resections and we expect these will be followed by others. In other words, it is not expected that there will be a lessened incidence of definitive surgery following nonoperation over that expected after operative closure of perforated ulcers.

EVALUATION

In general our results have been satisfactory. Nevertheless, there are many deficien-

cies in the principle of nonoperation. Attention must be called to one of these which has been completely overlooked so far in the statistical recordings.

During the time that the 24 patients were under observation and the 220 patients were operated upon for emergency closure of perforated ulcer, another group completely escaped analysis. This group lies hidden in all reports so far made on this subject. It consists in the group of patients whose condition was misdiagnosed or those in whom the diagnosis was obscure. Another group may be added to this, those patients admitted to the hospital in a moribund condition.

In our particular "hidden group" there were 22 patients who had perforated peptic ulcer not operated upon. These perforations were proved by x-ray examination or at autopsy in all but 2 cases. All 22 patients died. Nine were not operated upon because they were too sick and could not be revived sufficiently for operation. Most of these deaths occurred at the Indianapolis General Hospital where large scale emergency blood transfusion is still an unsolved problem. In the remaining 13 perforations operation was not performed because the diagnosis was obscure, often suggesting a medical condition or at least one not requiring emergency operation (coronary disease, pancreatitis, cholecystitis, mesenteric thrombosis).

Here then is a group of 22 patients with ruptured peptic ulcers, all of whom died without operation. It is fully admitted that some of these extremely sick patients should not and would not have died if sufficient blood had been available for treatment. This still leaves a sizable number of deaths from undiagnosed perforated ulcers. This group is not reported and not mentioned in the previously reported series. It would seem most unlikely that ours is the only group who encounters moribund patients or those with undiagnosed perforated peptic ulcer.

It is difficult to know where to place this "hidden group" statistically. They should not be included with those cases which were known from the first to be perforated peptic ulcer. Nevertheless, they must appear in each report of cases of perforated ulcer not operated upon or the true picture of the problem is lost. In the present report the importance of this group is magnified by the fact that it approximated in number the group electively treated by nonoperative therapy. A better perspective is obtained by indicating that the "hidden group" constitutes 8 per cent of all peptic ulcer perforations seen during the period under consideration. This is somewhat higher than current figures. Nevertheless, we must accept the fact that a small group of patients will die with misdiagnosed ulcer.

Furthermore, it is suggested that the "hidden group" be taken into consideration in evaluating the results in patients treated by operation as well as in those in whom operation is omitted. It is quite unfair to report only those patients going through the operating room while the pathologist may have a few coming from the medical or other surgical wards. In the cases treated by operation at Cincinnati General Hospital reported by McElhinnery and Holzer, 4 per cent were undiagnosed when the patients were first seen on the medical or psychiatric services. The number of cases which reach the autopsy table misdiagnosed or unoperated upon was not stated.

DISCUSSION

Observation of our relatively few patients has indicated some inescapable conclusions. We are convinced that purposeful nonoperative therapy has a definite place in the treatment of perforated peptic ulcer. The purpose of this discussion is an attempt to fix that place and to learn more of the usefulness of the treatment.

There are two fundamental principles which govern the treatment of perforated peptic ulcer. The first of these is closure of the perforation. This may be either by spontaneous or operative means. There is probably no particular advantage of one type of closure over the other. Death from a single gush of highly irritating but relatively innocuous gastric content must be very rare. Death usually results from continued leakage and contamination resulting in generalized peritonitis. Continuous gastric suction is a very important means of maintaining closure of the perforation and also of controlling distention. The second

principle concerns the treatment of the resultant peritonitis following perforation. This includes the administration of blood, electrolyte solutions, and antibiotics plus measures to keep the gut deflated. These measures are fairly well standardized and require no elaboration here. They will, however, be unsuccessful if closure of the perforation has not been obtained.

The recent discussions about nonoperative therapy have indicated the lack of necessity of operative intervention. These point out that operation is not always required and that very often the patient does very well without. The inference is made that perhaps the condition might well be abandoned by the surgeon. This is unjustified. Operation, in the patient with a recently perforated ulcer, may be compared to transfusion. In some cases it may be very definitely indicated; in others it may be completely superfluous. We believe it is the surgeon's responsibility to decide which patient should have operation as a therapeutic agent and in which one it may be safely omitted.

Taylor has indicated that patients unfavorable for nonoperative treatment are those who have a pyloric stenosis, a gross diffuse peritonitis, or who recently had a heavy meal. These are undoubtedly important features but not determining ones.

In the cases reported the decision as to operation rested upon whether or not the perforation seemed sealed off by limitation of signs of peritoneal irritation to the upper abdomen. This point immediately brings in the time factor. No one can tell at the onset of perforation if the ulcer will seal itself off or will remain open. Likewise, no surgeon would recommend waiting to find out—immediate operation is too safe.

If the patient is observed for the first time after 4 or 6 or more hours and if at that time physical signs indicate that peritoneal irritation is largely limited to the upper quadrants, with no evidence of spreading, then that patient can be treated safely with gastric suction plus the usual supportive measures. If there is any doubt about spontaneous closure, surely exploration must be included in the treatment.

A word should be included about the operation itself. Closure of a perforated peptic ulcer is an extremely simple, standardized procedure and requires but a short time to perform. When the patient's condition is stabilized with intravenous fluids and possibly transfusion, there should be a minimal mortality. Therefore, we should cease consideration of the operation as the all decisive factor. It is a part of the treatment. In some situations it may be all decisive but in others it is not.

SUMMARY

1. Nonoperative treatment in cases of perforated peptic ulcer has recently been presented as a safe and desirable form of therapy. These reports in many instances are misleading.

2. Twenty-four patients who received this form of therapy are included in this report. There were 2 deaths.

3. The reported cases of nonoperative treatment are in a sense selected since many are: (a) from military or other similar institutions, (b) late perforations in which recovery is already underway, (c) selected in the sense that they do not include the misdiagnosed or moribund cases.

4. The term "hidden group" has been chosen for those patients who died without operation under an incorrect diagnosis, or who were moribund on admission thus precluding consideration of any but supportive therapy. This group constituted 8 per cent of all hospital admissions for ruptured peptic ulcer in the present study. These deaths should be noted in the analysis of any form of ulcer therapy under discussion, whether it be operative or nonoperative.

5. A study of nonoperative treatment indicates that the operative suture of perforation of a peptic ulcer is not always the decisive factor in whether the patient lives or dies. The important point is closure of the perforation and in many cases this may be spontaneous. Operation may be omitted in those cases in which it is certain sealing off of the perforation has occurred.

6. Difficulty arises in determining just which patients require operation as a part of therapy. The following recommendations

seem justified: (a) All patients seen early with no indication of localization should have immediate operation. The hazard of waiting to see if a perforation will seal spontaneously is greater than the danger of operation. (b) Those patients seen some hours after perforation in whom there is definite evidence that the perforation has been sealed off (good general condition, soft lower abdomen) may safely have gastric aspiration and supportive therapy alone. (c) Operative exploration is mandatory if there is doubt as to whether spontaneous sealing has occurred or if the diagnosis is uncertain.

7. Subdiaphragmatic abscess as a complication seems to be definitely more frequent in the group not operated upon.

8. There is no reason to believe that non-operation results in fewer subsequent operations for the relief of the ulcer diathesis.

9. Whether operation is used or not, strict attention must be given to treatment of the peritonitis and continued deflation of the bowel.

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GALLSTONE ILEUS

Report of Eight Cases

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INTESTINAL obstruction due to gallstones is rare. Although, in practically all cases the obstruction is simple in type, uncomplicated by compromise of the blood supply or gangrene of the bowel, the mortality has none the less ranged around 30 to 50 per cent (1, 4, 6), as compared to a mortality of around 5 to 7 per cent (8) in cases of of simple intestinal obstruction due to other causes such as adhesions, strictures, carcinoma, or hernia.

While factors which contribute to this high mortality become apparent on further analysis of the type of patient usually having gallstone obstruction, it nevertheless seems reasonable that if the physician is kept constantly aware of the possibility of this type of obstruction, the mortality will be markedly reduced.

The purpose of this paper is to report the experience with 8 cases of gallstone ileus occurring in the Hospital of the University of Pennsylvania between December 1939 and February 1951. During this period there were 549 cases of proved mechanical intestinal obstruction, giving an incidence of 1.4 per cent for gallstone ileus. This is in keeping with the incidence reported by most authors (4, 6), although some have reported as high as 4 per cent (1) to 6 per cent (3).

CASE REPORTS

Three of the patients (Table I, Cases 1, 2, and 3) were operated upon within 4 hours after admission to the hospital. A representative case in this group follows.

BK, Chart No. 81103, a 63 year old white female, was admitted to the University Hospital complaining of severe intermittent, recurrent, crampy abdominal pain, nausea, and vomiting of 4 days' duration. She had been severely constipated for a similar period of time. The vomitus had become fecal in character prior to admission. For the past 10 years she had had occasional recurrent bouts of epigastric and right upper quadrant pain and vomiting, excessive flatulence, and intolerance to fried or fatty foods. There was a history of jaundice during one of these attacks about 6 months before admission to the hospital. She was known to have hypertensive heart disease. She had an appendectomy at the age of 26.

Examination on admission revealed an obese, dehydrated, elderly white female who was vomiting a brownish, foul-smelling fluid every 15 to 30 minutes. The temperature was 98.6 degrees F., pulse 88, and the blood pressure was 166/102. Examination of the abdomen revealed slight distention, tenderness to palpation in both lower quadrants, and hyperactive peristalsis with occasional rushes.

The white blood cell count was 10,100, and a survey film of the abdomen revealed dilated loops of small bowel with air and fluid levels. A diagnosis of small bowel obstruction, probably on the basis of postoperative adhesions, but possibly on the basis of a nonopaque gallstone, was made and operation was carried out within 4 hours after admission, following the administration of intravenous fluids and the passage of a Miller-Abbott tube.

At operation through a right lower abdominal transverse incision a large gallstone 3 by 4 by 3 centimeters was found obstructing the jejunum about 3 feet below the ligament of Treitz. Palpation revealed an inflammatory mass in the region of the gall bladder and care was taken to avoid breaking down the adhesions in this area. The bowel was opened longitudinally and closed transversely. Her convalescence was smooth and she was discharged on the eighth postoperative day. She returned 2 months later at which time a cholecystectomy, choledochostomy, and excision of a cholecystoduodenal fistula was carried out. Convalescence was again smooth.

All 3 of the patients in this group had a definite history of gall bladder disease. In the case history cited, the presence of an obturating gallstone as the cause for the intestinal obstruction was considered in the preoperative diagnosis because of the previous history and the intermittent recurrent bouts of obstruction gradually progressing to complete obstruction. It will be noted (Table I), that 2

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TABLE I.—EIGHT CASES OF GALLSTONE ILEUS

Case No.	Chart No.	Age, sex	Duration of symptoms		Location of gallstone	Procedure	Died	Comment	Previous history of gallbladder disease
			Onset to adm., days	Adm. to operation, hours					
1	81103	63F	4	4	Upper jejunum	Enterotomy	o	Subsequently had cholecystectomy, choledochostomy and excision cholecystduodenal fistula	Yes
2	71422	64F	7	4	Lower ileum	Enterotomy	o	Subsequently had cholecystectomy, choledochostomy, and excision cholecystduodenal fistula	Yes
3	81396	75F	4	4	Upper jejunum	Enterotomy	o	Uneventful recovery. No further procedure	Yes
4	67607	66F	5	20	Lower ileum	Enterotomy, proximal Witzel enterostomy	o	Recovery uneventful. No further procedure	Yes
5	40957	72F	7	30	Upper ileum	Enterotomy	o	Convalescence satisfactory. No further procedure	No
6	67984	70F	7	40	Lower ileum	Enterotomy	o	Convalescence satisfactory. No further procedure	Yes
7	90225	62F	5	144	Lower jejunum	Enterotomy	o	Convalescence satisfactory. No further procedure	Indefinite
8	82195	88F	4	48	Upper jejunum	Biopsy, carcinoma of gall bladder	+	Continued to be obstructed in postoperative period and died 3rd postoperative day. Autopsy showed gallstone obstruction	Yes

of these 3 patients had subsequent cholecystectomies, choledochostomies, and repair of the cholecystoduodenal fistulas. All 3 of the patients were operated upon with a diagnosis of small bowel obstruction and in only 1 was the true etiologic agent considered in the preoperative diagnosis.

Three of the patients (Table I, Cases 4, 5, and 6) were operated upon between 20 and 40 hours after admission. Case 6 is representative of this group:

AK, Chart No. 67984, a 70 year old white female, was admitted to the University Hospital complaining of pain in the abdomen. Seven days before admission she had sudden, severe, abdominal pain, nausea and vomiting occurring in the middle of the night. These symptoms had continued up until admission and had gradually increased in severity. She had been constipated since the onset of the pain. She stated that she had passed a small tarry stool 2 days before admission. She had a past history of intermittent, recurrent bouts of postprandial epigastric and right upper quadrant distress and occasional vomiting coming on usually around 1 or 2 o'clock in the morning. She had had a hysterectomy 16 years ago.

Examination revealed an obese, dehydrated, elderly female complaining of severe abdominal pain. The temperature was 99.4 degrees F., and the pulse was 96. There was diffuse abdominal tenderness to palpation and rebound tenderness in epigastrium. Peristalsis was physiological. White blood count was 13,000.

Soon after admission to the hospital she began to vomit a fecal-like material and she was immediately placed on suction drainage and intravenous fluids. It was felt that she had a partial intestinal obstruction progressing to complete obstruction probably on the basis of adhesions or large bowel cancer. The morning following admission, a barium enema was performed and showed no obstruction of the colon but did show distended loops of small intestine. A Miller-Abbott tube was immediately passed but the patient continued to vomit, decompression was not accomplished, and she was operated upon 40 hours after admission with a diagnosis of small bowel obstruction probably on the basis of adhesions. At exploration through a muscle splitting right midrectus incision an obturating gallstone measuring 2.5 centimeters in diameter was found in the ileum 4 feet from the ileocecal valve. A longitudinal incision was made in the ileum on the antimesenteric border overlying the stone and the gallstone was removed. No attempt was made to explore the biliary area. The ileal rent was closed in transverse direction, and the abdomen was closed. Her convalescence was marred by a short period of disorientation, but was otherwise uneventful and she was discharged from the hospital on the twelfth postoperative day. No subsequent operation was performed.

Delay between admission and operation occurred in this group for a variety of reasons. In the case cited, the patient was believed to have a large bowel obstruction, incomplete in nature, and only when a barium enema on the morning following admission revealed distend-

ed loops of small gut was the true nature known. Delay for 30 hours occurred in Case 5 in order better to prepare the patient for operation. Roentgen examination soon after admission had revealed small intestinal obstruction, but the patient was severely dehydrated, acidotic, and had severe heart disease with auricular fibrillation. Appropriate parenteral fluids and digitalis were administered, and constant suction was applied through a Miller-Abbott tube. Operation was carried out at what was believed to be the earliest optimum time. In Case 4, delay for 20 hours occurred while trying to pass a Miller-Abbott tube. This maneuver was unsuccessful, the patient became sicker and more distended and operation was therefore performed.

Due to delay in diagnosis, 6 days elapsed between admission and operation in Case 7.

FB, Chart No. 90225, a 62 year old white female, was admitted to the hospital complaining of severe crampy epigastric pain, nausea and vomiting, and constipation of 5 days' duration. There was a history of indigestion for many years but no definite evidence of gall bladder disease. She was known to have hypertensive arteriosclerotic heart disease and diabetes.

Examination on admission revealed a severely dehydrated, elderly, obese female in peripheral vascular collapse. The temperature was 98 degrees F., and the pulse was 118 and of poor quality. There was questionable upper abdominal tenderness but no distention and no hyperactive peristalsis. It was the impression after examination that she was in diabetic acidosis but this was not confirmed by the laboratory studies. The hemoglobin was 120 per cent, the white blood count was 19,100, the blood urea nitrogen was 133 milligrams per cent, carbon dioxide combining power 43 millimols per liter, and the chlorides 74 milliequivalents per liter. The urine sugar was negative. She was immediately placed on intragastric suction and intravenous fluids and improved on this regimen. She did, however, continue to drain large amounts from the Levin tube and a barium swallow was performed which showed an obstruction in the duodenum believed probably to be due to an ulcer. After 3 days of further preparation with intravenous fluids and blood, and stabilization of her diabetes, she was operated upon through an upper midline incision. There were dense adhesions in the gall bladder area. The upper one-third of the small gut was distended and an egg-sized gallstone was found completely obstructing the upper jejunum. The gallstone was removed by enterotomy and she was discharged on the fifteenth postoperative day.

The presence of further complicating factors is demonstrated by the final case:

AT, Chart No. 82195, an 88 year old white female, was admitted to the hospital complaining of abdominal pain of some 12 days' duration, and of nausea, vomiting, and obstipation of 4 days' duration. The vomitus had become fecal in character and in addition contained a few streaks of bright red blood. She had been admitted to the hospital 2 years previously complaining of inability to swallow anything for approximately 1 year. Studies at that time revealed a large esophageal diverticulum, a large gallstone present within the gall bladder, and marked degenerative changes in the spine. Because of her age and associated conditions it was felt that operation was not indicated at that time. No specific therapy was given. In addition, she had a large umbilical hernia which had been present for a period of 45 years, always rather easily reducible until the present admission.

Examination on admission revealed a dehydrated, acutely ill, elderly, obese female. The temperature was 98 degrees F., pulse 86, and the respirations were 20. The abdomen was slightly distended, and there was a tender palpable mass in the right upper quadrant. In addition, there was an irreducible, slightly tender, umbilical hernia. Peristalsis was not obstructive in character. Survey films of the abdomen revealed what was interpreted as a possible closed loop obstruction with a small amount of gas and fluid in one loop. The loop was thought possibly to be in the umbilical hernia. The umbilical hernia was manually reduced soon after admission, constant suction was applied to the stomach through a Levin tube, and parenteral fluids were administered. On such a regimen her abdominal signs disappeared except for the slightly tender right upper quadrant mass. Around 24 hours after admission, however, her signs and symptoms returned, and, in addition she had drained around 2,000 milliliters of fluid through the Levin tube. Her signs and symptoms progressed and she was operated upon around 48 hours after admission with the diagnosis of probable acute exacerbation of chronic calculous cholecystitis. Upon entering the abdomen through a right subcostal incision a hard matted obviously carcinomatous mass was found to be present in the right upper quadrant and the liver was studded with many metastatic lesions. A diagnosis of carcinoma, probably of the gall bladder, with widespread metastasis was made, a biopsy was taken from the liver, and the abdomen was closed.

During the postoperative period she continued to drain copious amounts from the Levin tube. On the third postoperative day she suddenly vomited, aspirated the vomitus, had cardiac arrest, and died. At necropsy she was found to have complete obstruction of the intestine 30 centimeters distal to the ligament of Treitz with a large gallstone 5.5 by 4.5 by 3.0 centimeters with several smaller calculi firmly adherent. Other findings were a primary carcinoma of the gall bladder with widespread metastasis, calculous cholecystitis, choledochoduodenal fistula, and bronchial and bronchiolar obstruction due to aspirated gastric contents.

DISCUSSION

The hazards attendant upon the diagnosis and management of gallstone obstruction may be readily seen by the foregoing case presentations. The vast majority of the patients are elderly, obese, females (9) usually with associated complicating conditions such as organic heart disease or diabetes. All of the patients in this series were females and the average age was 70 years, the youngest patient being 62 years and the eldest 88 years of age. In at least 3 of the patients diagnosis and management was severely complicated by the presence of other conditions. Particularly was this true in the patient who died. A large esophageal diverticulum, an irreducible umbilical hernia, and a palpable right upper quadrant mass were prominent in obscuring the diagnosis. A definite past history of gall bladder disease was obtained in 6 of the 8 patients. One of these was known to have gallstones by previous cholecystogram, and another had attacks of jaundice.

The presenting symptomatology is usually characteristic of a mechanical intestinal obstruction usually low in the intestinal tract. There is a history of crampy abdominal pain, nausea, vomiting, and constipation progressing to obstipation over a period of several days to a week. The long duration of symptoms before these patients present themselves is probably of even greater importance than the age as a factor in mortality. Foss and Summers reported that the average duration of symptoms in their patients who died was 5.2 days. The average duration of symptoms in this series was 5.4 days, ranging between 4 and 7 days. Fecal vomiting was stated as being present in 4 of the 8 patients on admission to the hospital. When one adds to the long duration of symptoms, the time spent in the hospital in attempting to make the diagnosis prior to operation then the long delay between onset of symptoms and operation becomes even more apparent.

The patient may present in a state of serious dehydration and electrolyte imbalance consequent to the vomiting and this in turn further complicates the picture. While abdominal distention may be present it is usually obscured by the obesity of the patients, and accurate evaluation can only be obtained by a survey film of the abdomen. This will indicate whether or not distended loops are present and may even reveal the cause of the obstruction. Rigler, Borman, and Noble have reported the roentgenologic criteria which when present lead to a positive diagnosis of gallstone obstruction, namely: (1) air or contrast media in the biliary system; (2) direct visualization of the stone; and (3) roentgenologic evidence of intestinal obstruction.

Almost invariably gallstone obstruction is preceded by the development of an internal fistula between the biliary system and the gastroentestinal tract, although, Murphy reported a case in which the obstructing calculus was considered to have forced its way through an enormously dilated common duct. Since the first and second portions of the duodenum are most closely related anatomically to the gall bladder, a cholecystoduodenal or choledochoduodenal fistula (as in Case 8) are the most common. A cholecystocolic fistula may occur but it is rare and rarely produces obstruction. Once the stone has entered the duodenum, it may be arrested at any point during its transit, thereby producing obstruction. Although the most frequent site of the lodgement has been reported in the distal ileum (1, 4, 6) it will be noted (Table I) that in 4 of the cases herein reported the obstruction was high in the jejunum.

The management of these patients is in no way different from that of the management of any patient believed to have intestinal obstruction from any cause (2). A positive etiological diagnosis is of academic interest only and entirely secondary to correction of the associated physiological disturbances that occur in obstruction of the intestine. Oral intake should be immediately stopped and suction drainage instituted. In 6 of the patients in this series a Miller-Abbott tube was used, and a Levin tube was used in the remaining 2. Appropriate parenteral fluids should be started as rapidly as possible, the amount and type to depend largely on the results of laboratory studies such as hemoglobin, blood chlorides, blood urea nitrogen, carbon dioxide combining power, blood sugar, and serum sodium and potassium.

The importance of obtaining survey roentgen films of the abdomen in both the anteroposterior, upright, and lateral recumbent positions cannot be emphasized too strongly. Most of these patients are obese with protuberant, flaccid abdominal walls, and distention may not be noticeable on examination. Only by roentgen examination can the true picture be demonstrated, and the actual etiological agent may even be shown. In 1 of the patients in this series (Case 6) the diagnosis was appreciably delayed by failure to obtain a roentgenogram. When the diagnosis is established operation should be carried out at the earliest possible time.

More often preoperative findings indicate intestinal obstruction but do not indicate the etiology. Under these circumstances the decision to operate must be arrived at as in any other type of mechanical obstruction. Obviously, many of these patients will arrive at the hospital in a severely dehydrated state. Furthermore, they are usually in an age group in which diabetes, heart disease, and other serious handicaps are relatively frequent. Such conditions must be recognized and given due consideration in the over-all management of the patient. It is believed, however, that restoration of blood volume, compensation for fluid losses, the inauguration of effective antidiabetic therapy, and even digitalization can be accomplished in a few hours if the full facilities of a modern hospital can be drawn upon. Suction drainage, preferably through a Miller-Abbott tube can be of inestimable value in decreasing distention with all its untoward effects on plasma volume, hepatic circulation, and respiration. This method should not, however, be permitted to lead to unjustified delay in operation. If the patient fails to show definite improvement within a period of hours, then no further delay should be countenanced. Obviously, if the obstruction is known to be on the basis of a gallstone, operation must be carried out at the earliest possible time. In 6 of the patients in this series the preoperative diagnosis was intestinal obstruction and in only 1 of these was a gallstone considered as the etiologic agent. In Case 7 the preoperative diagnosis was duodenal ulcer with obstruction, and in Case 8 the preoperative diagnosis was acute cholecystitis.

The operative procedure employed in the 7 patients who survived was longitudinal incision of the intestine over the stone, removal of the stone, and closure of the bowel in transverse direction. In 1 of these, because of the marked distention, a Witzel type enterostomy was performed proximal to the enterotomy. In the remaining case, operation was performed through a right subcostal incision. The presence of gallstone ileus was obscured by the finding of a large carcinomatous mass in the region of the gall bladder with massive metastases to the liver, and the abdomen was closed without exploration of the bowel. It should be emphasized that at the time of removal of a gallstone rapid search of the gut should be carried out to exclude the presence of a second obstructing stone. Foss and Summers reported the case of a patient in which one stone was removed but she expired on the eighth postoperative day and at necropsy a second obstructing stone was found. If a faceted stone is present the possibility of multiple stones should be kept in mind and a search made for them. If the small bowel distention is of severe proportions and if passage of a long tube through the oropharynx has been unsuccessful, a Witzel enterostomy may be indicated. In no case was any effort made to explore the biliary area or to drain it at the time of operation. The enterotomy was accomplished as rapidly as possible and the abdomen was closed.

The mortality in gallstone obstruction has been extremely high, ranging around 30 to 70 per cent in most series (1, 4, 6). McLaughlin tabulated the mortality statistics of 14 different series and reported 4 personal cases of gallstone ileus without a mortality. The mortality in this group of cases was 12.5 per cent.

The factors responsible for the high mortality have been mentioned previously. The improvement in mortality in the cases herein reported is probably a logical result of a better understanding of the pathologic physiology of intestinal obstruction rather than any decrease in the length of time between onset of symptoms and operation or any improvement in operative technique. While the condition is

admittedly rare, the associated high mortality when it does occur is another argument in favor of removal of the calculous gall bladder. As McCready and Seybold have pointed out, the complications of cholelithiasis cannot be anticipated or prevented except by surgical removal of the stone containing gall bladder.

SUMMARY AND CONCLUSIONS

1. Eight cases of gallstone ileus occurring in the Hospital of the University of Pennsylvania between 1939 and 1951 have been presented. One of these patients died.

2. Gallstone ileus should be strongly suspected in an elderly obese patient presenting with the signs and symptoms of intermittent recurrent obstruction progressing to complete obstruction and in which a history of gall bladder disease is obtained.

3. The high mortality which has occurred in this group of patients has been a result of age, obesity, associated complicating conditions, too extensive surgery, and, probably most important, delay in diagnosis.

4. If the physician is kept constantly aware of the occurrence of gallstone ileus with a resultant decrease in the time lapse between onset of symptoms and institution of active treatment, then it is believed, the mortality will be appreciably decreased.

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STUDIES IN EXPERIMENTAL FROSTBITE

IX. Rapid Thawing and Prolonged Local Cooling in the Treatment of Frostbite Resulting from Exposure to Low Ambient Temperature

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EXPERIMENTAL studies carried out during recent years have clarified our understanding of the underlying basic physiopathology of frostbite and have shed light upon its proper treatment.[1] Up to the present time direct immersion of a portion of the body in a freezing mixture and contact spot freezing have proved the only dependable methods of producing frostbite in experimental animals from the standpoint of uniformity and reproducibility of the resultant injury. Since human frostbite is so rarely incurred in similar fashion, some have questioned the validity of transferring conclusions drawn from such experimental observations to the problem of frostbite in man. The recent demonstration by Blair and his associates that freezing injuries can be inflicted upon rats and rabbits by exposing them to low ambient temperatures has fortunately made available a method much more akin to the manner in which human freezing injuries are commonly sustained. The present study is concerned with evaluation of two controversial methods of treatment, rapid thawing and prolonged local cooling, in frostbite which develops in the unanesthetized mouse upon exposure to low environmental temperature.

METHODS

Domestic albino mice usually weighing between 19 and 25 grams were placed in individual small wire containers and exposed to low temperature in an ordinary domestic type deep-freeze unit. The ambient temperature ranged from −19 to −10 degrees centigrade and the period of exposure from 40 to 80 minutes. By exposing an additional mouse every 5 minutes in any given experiment, time was available after removal of each animal from the cold environment for making certain observations, such as the extent of freezing and the interval before thawing, and for carrying out any desired treatment. Alternate animals removed from the deep-freeze unit were treated, the others being kept for control observations. Usually 20 animals were exposed during each experiment, half being treated and half kept as controls.

In those animals treated by rapid thawing the solidly frozen tails were immediately immersed in a water bath kept at 42 degrees centigrade and left in it for 2 minutes. The tails of the control animals were allowed to thaw spontaneously at ordinary room temperature (27 to 30°C.). Both groups of animals were then kept in a room maintained constantly at a temperature of from 25 to 26 degrees centigrade.

In the experiments concerned with local cooling of the frozen part, each animal was placed immediately in a small wire cylinder constructed in such a way as to keep the tail of the mouse in a glass tube immersed in an ice water bath with a temperature of from 1 to 3 degrees centigrade.[2] The animals were removed from this apparatus after the tail had thus been kept chilled for 24 hours. The control animals were placed for 24 hours in similar wire cylindrical containers with the tail in an open ended glass cylinder. These animals as well as those in the treated group

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[1] These contributions have been recently reviewed (4, 5) and references to most of the important publications are cited in these reviews.

[2] This apparatus has been used in a previous study and is adequately described in the report of this work (3).

were kept thereafter in a room constantly maintained at a temperature of from 25 to 26 degrees centigrade. Both groups were housed in ordinary mouse cages after the first 24 hours.

No animals were discarded except those which died immediately from the exposure, those few which died within such a short time after freezing that it was impossible to determine how extensive the loss of tissue would ultimately have been, and those few in which solid freezing of the tail did not occur. The length of the tail of each mouse was determined at the beginning by measuring the distance between the tip of the tail and the hairline at its base. Each animal was inspected daily and the extent of the necrosis in centimeters was recorded, as well as a rough estimate of the degree of edema present. Final measurements of the extent of necrosis were made approximately 2 weeks after the injury. By this time the gangrenous portion had separated spontaneously in most of the animals, and its extent could be determined by subtracting the length of the remaining viable tail from the original measured length. In the few in which spontaneous amputation had not yet taken place the line of demarcation was clear and had not changed for a number of days.

RESULTS

General observations. Preliminary studies demonstrated that most animals weighing less than 19 grams died following exposure of approximately 1 hour to temperatures of from −19 to −10 degrees centigrade, often before the tail became solidly frozen. In contrast, most of the mice weighing from 19 to 25 grams survived the exposure and sustained solid freezing of the entire tail. Longer periods of exposure resulted in a high mortality, and even with the periods used 47 mice died during the exposure and only 165 frostbitten mice survived to serve as the experimental animals of the present study. In a few additional instances a portion, but not all, of the tail was frozen; these animals were not included either in treated or control groups. In one-third of the experimental animals one or more feet also became frozen, the forefeet less often than the hind. A few of these animals ultimately lost tips of toes from gangrene. Animals with freezing of the feet as well as the tail were about equally divided among the treated and control groups. Freezing of the ears was not observed.

Results of rapid thawing. Thirty-seven mice which incurred solid freezing of the entire tails were treated by immediate rapid thawing, while 37 similarly injured mice served as untreated controls (Table I). The two groups were comparable in weight, length of tail, and severity of the exposure. The control group averaged 21.6 grams in weight while the treated mice averaged 21.4 grams. The overall length of tail was almost precisely the same, being 8.77 in the untreated group and 8.76 centimeters in the treated group. The temperature at which the animals were exposed ranged from −15 to −10 degrees and the two groups did not differ in this respect. Three untreated animals and 2 of the treated group were exposed for 55 minutes. Eight untreated animals and 10 of the treated group were exposed for 60 minutes. Twenty-six of the untreated animals and 23 of the treated group were exposed for 55 minutes. Two of the treated mice were exposed for 70 minutes. Thawing of the tails in the untreated group took place in from 40 to 162 seconds; the average time was 108 seconds.

The mice treated by rapid thawing fared considerably better than the untreated control animals. The mean loss of tissue was 0.98 centimeter or 11.2 per cent of the mean total length of tail, while the mean loss in the other group was 1.98 centimeters or 22.6 per cent. Twelve or 32.4 per cent of the treated mice sustained no loss of tissue at all. Such an excellent result obtained in only 4 (10.7 per cent) untreated animals. A good result with loss of no tissue, or no more than the distal 1 centimeter of the tail, was obtained in 25 of the treated group (67.7 per cent) and in only 10 of the control animals (27 per cent).

Results of prolonged local cooling. Forty-five mice which incurred solid freezing of the entire tail were treated by keeping the injured tail chilled for 24 hours, whereas an equal number serving as controls were restricted

TABLE I.—RESULTS OF RAPID THAWING AND PROLONGED LOCAL COOLING IN THE TREATMENT OF FROSTBITE OF THE TAILS OF MICE

Untreated group				Treated group			
No. of animals	Mean loss of tissue in cm.	Per cent with excellent result	Per cent with good or excellent result	No. of animals	Mean loss of tissue in cm.	Per cent with excellent result	Per cent with good or excellent result
Rapid thawing							
37	1.98	10.7	27	37	0.98	32.4	67.7
Prolonged local cooling							
45	2.73	11.1	26.6	45	4.35	2.2	15.5

for a like period in similar apparatus without cooling the tail (Table I). The two groups were comparable in weight, length of tail, and severity of exposure. The control group averaged 21.3 grams in weight while the treated group averaged almost precisely the same (21.2 grams). The mean overall measured length of tail was 8.02 centimeters in the control group and 8.16 centimeters in the treated group. The temperature at which the animals were exposed ranged from —19 to —12 degrees and there was no difference in the two groups with respect to the severity of the cold to which they were exposed. There was no significant difference in the duration of the exposure in the two groups. For example, 18 of the control group and 19 of the treated group were exposed for 40 or 45 minutes. Fourteen of the control animals and 13 of the treated group were exposed 50 or 55 minutes. Eight of the control animals and 11 of the treated group were exposed for 60 or 65 minutes. Five of the control animals were exposed for from 70 to 80 minutes and 2 of the treated group.

Prolonged local cooling of the frostbitten tail resulted in a trend toward increased tissue damage. The mean loss of tail resulting from gangrene was 4.35 centimeters or 53.3 per cent of the mean total length of tail in the group treated by prolonged cooling as compared with 2.73 centimeters or 34 per cent in the control group. In only 1 animal was there no loss of tissue (2.2 per cent) while such an excellent result was observed in 5 of the control group (11.1 per cent). Only 7 mice in the treated group sustained no loss of tissue or no more than 1 centimeter (15.5 per cent). Such a good result obtained in 11 of the control group (24.4 per cent).

DISCUSSION

In view of certain observations it seemed to us unlikely that the studies previously carried out upon animals in which frostbite was inflicted by immersion of a portion of the body in a freezing mixture or by spot contact freezing were without valid relationship to the problem in man. First, no essential difference either in the resultant tissue necrosis nor in the tendency toward persistent vasomotor alterations had been noted between cases of high altitude frostbite in which freezing was often almost instantaneous, on the one hand, and cases developing after prolonged exposure upon the ground, on the other. Secondly, observations in experimental frostbite had convinced us that, in spite of considerable variability in the period of exposure before onset of freezing, the process of freezing, once it begins, spreads with remarkable rapidity to involve the entire area which eventually becomes frozen. My associates and I quickly learned from our early experiments that rather reliable and reproducible results as far as tissue necrosis was concerned could be obtained by standardizing the temperature to which the tissues were exposed and the duration of actual freezing. The injury could not be standardized by making constant the total period of exposure. In the present study concerning exposure of unanesthetized animals to low ambient temperatures it was also noted that freezing of tissues took place very rapidly once it began. It appears entirely likely that the same holds true

for man and that even though freezing may be preceded by hours or days of exposure to a cold atmosphere the actual process of freezing is itself quite rapid. In spite of these considerations, however, it was obviously desirable to learn whether the results of treatment of experimental frostbite incurred as the result of exposure to low ambient temperature would be similar to those which had been obtained in the case of freezing injuries resulting from immersion in freezing mixtures.

Studies carried out in the present investigation demonstrate that such is the case. Immediate rapid thawing of the frozen part and prolonged local cooling were selected as the therapeutic methods to be tested for two reasons. In the first place, they constitute the two most controversial measures to be applied in the emergency treatment of frostbite. In the second place, rapid thawing has proved consistently to be the most effective means of reducing the incidence and extent of tissue necrosis resulting from experimental frostbite. The clear-cut benefit of rapidly thawing the still frozen part by transient application of warmth just exceeding body temperature has been demonstrated in experiments with frostbite of tails, ears, and feet. It has been demonstrated in experiments in mice, rats, rabbits, and dogs. Conversely, in the few carefully controlled observations which have been made prolonged local cooling has been shown to be of no benefit but indeed to tend to result in increased tissue damage.

The present studies were entirely confirmatory of these previous results. Rapid thawing of the frozen tails of mice decreased the tissue damage to such an extent that the mean loss was only half as great as in the control animals. As in previous studies, the results have been further analyzed by grouping together as excellent results those in which all tissue necrosis was prevented and as good those in which gangrene was limited to the tip of the tail (1 cm. or less). The validity of the first grouping is obvious. The second is felt to be of importance since limitation of loss of tissue to the distal parts results in far less dysfunction than if the damage is more extensive. For example, the person who loses only toes or portions of toes suffers little disability, while gangrene involving more proximal portions of the foot generally necessitates a major amputation with its resultant handicap. In the present study rapid thawing increased the percentage surviving with no loss of tissue from 10.7 to 32.4 and the percentage in which tissue damage was prevented or was limited to the distal centimeter of tail from 27 to 67.7. All of these results are highly significant when analyzed statistically.[1]

Prolonged local cooling, in contrast, was of no benefit but rather seemed to increase the resultant gangrene. The mean loss of tissue was 2.73 centimeters in the control and 4.35 centimeters in the treated group. The percentage in which no loss of tissue was sustained was 11.1 in the untreated and 2.2 in the treated animals, while the percentage in which either no tissue was lost or in which the necrosis was limited to the distal centimeter similarly was greater in the control group (26.6 as compared with 15.5 per cent). These changes though not of definite statistical significance reveal a trend toward an increase in resultant tissue necrosis in those animals treated by prolonged local cooling.[2]

A striking parallelism is noted when one compares these results obtained in treating frostbite which occurs spontaneously in unanesthetized and unrestricted mice exposed to low ambient temperatures with results of similar studies dealing with the treatment of frostbite induced by immersion of the distal

[1]The significance of the difference of the mean loss of tissue in the two groups was tested by the t ratio technique. The mean tail loss in the control animals is significantly greater than that in the group treated by rapid thawing beyond the 0.01 level of confidence. The significance of the difference in the number with excellent and good or excellent results in the two groups was tested by the chi-square technique. The number with excellent results among those treated is significantly greater than among the control group beyond the 0.05 level of confidence. Similarly, the number with good or excellent results among the treated group is significantly greater than among the controls beyond the .001 level of confidence.

[2]When tested by obtaining the quotient of the difference of the means and the standard error of the differences, the difference in the mean loss of tissue in the two groups would appear to be significant. When tested by the t ratio technique, however, the mean tail loss for the group with prolonged cooling is greater than for the control group, but the difference is not sufficiently large to be attributed confidently to anything but chance. Due to the small percentage with excellent results in both groups the question of the significance of the difference cannot be reliably analyzed. When tested by the chi-square ratio there is no significant indication that the number with good and excellent results are obtained more frequently among the control than among the group treated by prolonged local cooling.

TABLE II.—COMPARISON OF RESULTS OF RAPID THAWING AND OF PROLONGED LOCAL COOLING IN FROSTBITE INDUCED BY IMMERSION OF THE DISTAL 6 CENTIMETERS OF THE MOUSE'S TAIL FOR 5 SECONDS AFTER SOLIDIFICATION IN AN ETHER-CARBON DIOXIDE MIXTURE KEPT AT —15° C. WITH RESULTS IN FROSTBITE RESULTING FROM EXPOSURE OF THE UNANESTHETIZED MOUSE TO LOW AMBIENT TEMPERATURE

Author	Untreated group				Treated group			
	No. of animals	Mean loss of tail in cm.	Per cent with excellent result	Per cent with good or excellent result	No. of animals	Mean loss of tail in cm.	Per cent with excellent result	Per cent with good or excellent result
Rapid thawing in frostbite inflicted by immersion of the tail in freezing mixture								
Lempke and Shumacker (3)	21	1.76	4.8	28.6	19	0.39	73.7	84.2
Finneran and Shumacker (2)	44	4.1	4.5	9.1	40	1.0	17.5	65
Shumacker, Radigan, Ziperman, Hughes (6)	64	4.04	6.3	14.1	60	1.16	23.3	61.6
Rapid thawing in frostbite resulting from exposure to low temperature								
	37	1.98	10.7	27.	37	0.98	32.4	67.7
Prolonged local cooling in frostbite inflicted by immersion of tail in freezing mixture								
Lempke and Shumacker (3)	21	1.76	4.8	28.6	19	3.7	0	0
Prolonged local cooling in frostbite resulting from exposure to low temperature								
	45	2.73	11.1	24.4	45	4.35	2.2	15.5

6 centimeters of the tails of anesthetized mice for 5 seconds after solidification in a carbon dioxide-ether mixture maintained at —15 degrees centigrade. The similarity in the results of rapid thawing is evident from Table II in which the present data are compared with those from the previously reported experiments. There is not available for comparison any entirely comparable study of prolonged local cooling in the treatment of frostbite induced by immersion of the tail in a freezing mixture. However, there has been reported a similar experiment in which the same method of local cooling was applied for 72 hours to the tails of mice after freezing the distal 6 centimeters by immersion for 5 seconds after solidification in a carbon dioxide-ether mixture kept at —15 degrees centigrade. These animals were compared with animals similarly injured but not restricted for a comparable time in the same apparatus. In these earlier studies prolonged local cooling resulted in the same definite trend toward an increase in the resultant damage as was noted in the current study (Table II).

This similarity is all the more interesting because of the essential difference in the manner in which the present and the former studies were conducted. The earlier investigations were designed to demonstrate any possible effectiveness of the therapeutic measure used. With direct immersion of parts of the body in freezing mixtures it is possible to inflict an injury so mild that there results no demonstrable permanent damage. It is also possible to produce damage so severe the outcome cannot be altered by any known treatment. Consequently the temperature of the freezing mixture and the period of freezing were selected so as to produce an injury in between these two extremes, one severe enough to result in permanent damage in a significant proportion of untreated animals and mild enough to permit improvement as the result of treatment. In contrast the injury inflicted in the current study was selected without regard to the possibility of altering the outcome by treatment. The animals were exposed for a period sufficiently long to bring about solid freezing of the entire tail and just short of a period of time which resulted in an almost universally fatal outcome.

CONCLUSION

It would seem that these studies demonstrate conclusively that frostbite in experi-

mental animals resulting from exposure to low ambient temperature responds favorably to rapid thawing of the frozen part and that prolonged local cooling is without benefit and is possibly of real harm. The parallelism between these results and those previously obtained in other experiments with a different method of producing frostbite suggest that the other experiments are valid and that conclusions drawn from them may have significance with regard to the problem of true freezing injuries in man.

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ACUTE INTESTINAL OBSTRUCTION IN ELDERLY PATIENTS

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IN A recent paper on surgical emergencies affecting elderly patients, based on a study of cases at The Goldwater Memorial Hospital of New York, the writer (4) reported 56 cases of acute intestinal obstruction. It was observed that the mortality rate in this condition developing in patients over 60 was 55 per cent. This high rate was attributed in large part to the fact that these patients, seen on this particular service, constituted an especially bad risk group, inasmuch as most of them were either inmates of the city home for aged and indigent persons or were already under treatment m some one of the city's free hospitals because of one or more of a variety of chronic diseases. These complicating conditions ran the gamut of disorders of the cardiovascular, renal, respiratory, and nervous systems and included hemiplegia, coronary infarction, cirrhosis, diabetes (some with amputations), tuberculosis, lues, crippling arthritis, parkinsonism, and a variety of metabolic disturbances and deficiency states.

The study of acute intestinal obstruction in the aged has been carried forward since the publication of the original report by the addition of further cases from the Goldwater service, now covering a 10 year period (1939 to 1949), and by the inclusion of the cases recorded at the Roosevelt Hospital during the same period.

The Roosevelt group numbered 63 cases. These patients, while of comparable age, were as a whole in far better condition than the Goldwater cases, coming from their homes to the hospital because of the emergency and being, for the most part, in passably good health for their years. A fair proportion of them were private patients. The mortality rate in this group was 53 per cent.

This similarity of mortality rate in two groups of patients, differing so widely in all circumstances but age, casts doubt on our assumption as to the effect of chronic disease on the outcome. The consistently high mortality led naturally to an inquiry as to the common denominators which might be accountable for it. For this reason the present paper combines the two groups for purposes of study and evaluation. The age range of the entire group was 60 to 102 years. The average age was 73 years.

These cases of acute intestinal obstruction fall naturally into etiological grouping. While all had certain features in common, each cause of obstruction presented some rather distinctive characteristics which set its group apart from the others in matters of symptomatology, physical and laboratory findings, treatment, and prognosis. Of the 123 cases here reported, acute mechanical intestinal obstruction had the following causes: hernia, 35; tumor, 31; adhesions, 20; foreign body, 11; volvulus, 10; and 16 were of undetermined origin.

HERNIA

Incarceration of gut within a hernial sac was the most frequent cause of acute intestinal obstruction. There were 35 such cases. The average age was 75 years. The oldest patient was 102 years. Twenty were men and 15 women. The types of hernia were distributed as follows: inguinal, 14; femoral, 11 (8 in women); umbilical, 6; incisional, 4. Twenty-two of the patients had obstructive symptoms for 1 day or less prior to operation. Of these, 4 died. There were 10 whose obstruction had lasted 3 days or more and 9 succumbed, 2 without operation.

The symptoms of which these patients complained were characteristic. They consisted of pain in the hernial region associated with irreducibility, increasing generalized abdominal pain, vomiting (which was usually early and persistent), distention, and obstipation. So acute were these manifestations that medical

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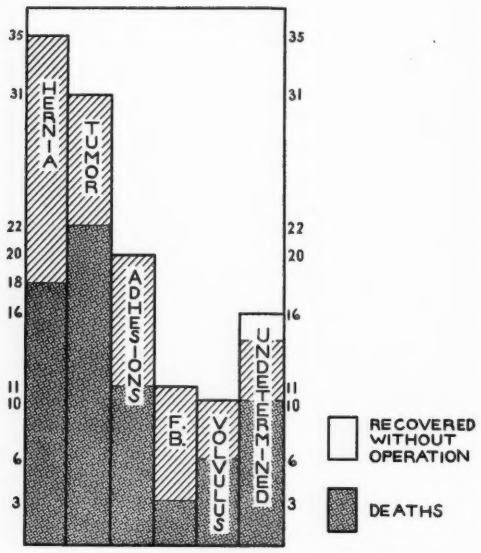

Fig. 1. Causes of obstruction in 123 cases.

advice was almost always promptly sought. In most instances surgery followed quickly. Notable exceptions to this were 2 patients whose obstruction had lasted 3 and 5 days respectively, who were admitted to the hospital in moribund condition and rapidly succumbed in spite of supportive measures.

In the presence of a recognized hernia, proving irreducible, the diagnosis was generally clear. There were 2 exceptions in which the diagnosis was not made promptly. In one an incarcerated recurrent inguinal hernia had been reduced with its sac en masse. In another, an incarcerated femoral hernia escaped detection until discovered by the pathologist. In those cases in which x-ray studies were made preoperatively the characteristic picture of small bowel distention was invariably shown.

The preoperative therapy was in most instances brief and followed a fairly consistent pattern, modified somewhat by the inclination of the surgeons concerned. Since there was no opportunity to rectify underlying chronic disease, the measures employed were fundamentally protective and supportive. Fluid and electrolyte losses were replaced as rapidly as could be done with due regard for circulatory inadequacies and antibiotic therapy started. The correction of blood volume deficit by transfusion was an important feature of preparation. The lower bowel was generally cleared by irrigation in those few instances in which repeated enemas had not previously been administered in unsuccessful attempts to overcome the obstruction. The stomach was emptied by irrigation, and suction was usually continued during the preoperative period.

The use of intestinal intubation to relieve the effects of obstruction prior to operation was pursued in several cases in one of the hospitals. A Miller-Abbott tube was employed for 1 day in the patient admitted after a 3 day obstruction who died without operation. It was used for 3 days following admission on 2 other 3 day obstructions without benefit. The patients were then operated upon and died. It was used for 1 day on a 4 day case in which the patient also succumbed after operation. On the other hand, it was used successfully for 4 days on a 3 day obstruction and for 4 days on a 1 day obstruction, both patients recovering after operation. Thus intestinal intubation appeared to be of value as a preoperative measure in 2 cases and failed in 4.

The types of anesthesia used varied considerably. In the Goldwater cases, under the influence of Dr. Rovenstine's teaching, cyclopropane was used in 14 of the operations. It proved a very satisfactory anesthetic. Seven were done with local anesthesia and one with local supplemented by pentothal. In the Roosevelt group 2 patients were operated on under local, the remainder with inhalation anesthesia—usually nitrous-oxide-ether or nitrous oxide with pentothal induction. There were no anesthetic accidents and the choice of agent had no discoverable bearing on postoperative respiratory complications or other morbidity.

Operation in all but 5 instances consisted in freeing of the obstructed loop, reduction of the hernia, and repair. All 5 of the patients requiring small bowel surgery because of strangulation and necrosis had femoral hernias. Three required resection of the damaged bowel with anastomosis. Two of these recovered. In another, a Richter's type femoral

hernia, closure of a gangrenous perforation was done, followed by fatality. Ileostomy was done in 1 case of unrecognized obstructing femoral hernia with fatal termination.

In 1 case of incisional hernia, the compromised gut returned to the abdomen at operation subsequently became gangrenous, resulting in death.

During the postoperative period Wangensteen suction was continued with either Levin or Miller-Abbott tube, fluids (usually by clysis) and blood were furnished as indicated, antibiotic drugs were continued, and the patients taken out of bed at the earliest moment.

Among the 11 patients who succumbed shortly following operation, the causes of death ascribed were as follows: pneumonia, 4; shock, 2; peritonitis, 2; sepsis, 1; congestive heart failure, 2. Five additional patients died from apparently unrelated conditions, i.e., 3 of coronary disease 13 months, 8 months, and 4 months postoperatively, 1 from decubitus ulcers and sepsis after an illness of 2 months, and 1 of ruptured esophageal varix. Including these in the postoperative fatalities gave a figure of 16 deaths in 33 patients operated upon. There were, besides, the 2 patients whose condition did not permit operation and who promptly died. These brought the figure to 18 deaths among 35 patients treated, a total mortality rate of 51 per cent. The directly related postoperative mortality was 33 per cent.

These observations led to the following impressions:

1. Considering the relatively low incidence of femoral hernias, the frequency of their causation of intestinal obstruction (as compared with inguinal hernias) was striking. The preponderance of women as sufferers from this catastrophe was noteworthy.

2. The hazards of femoral hernia were further emphasized in this study by the fact that 1 of 2 fatal cases not operated upon and all 5 strangulations requiring small bowel surgery occurred in femoral hernias. Moreover, almost half of the femoral hernias producing obstructions were strangulated. This fact stressed the desirability of a transabdominal surgical approach in such cases (5). The implication was that prophylactic repair of femoral hernias even in old people should have serious consideration.

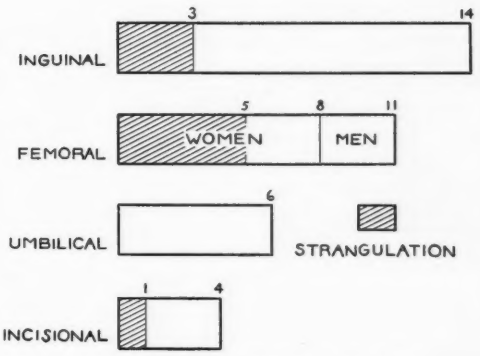

Fig. 2. Types of hernia causing obstruction in 35 cases and incidence of strangulation.

3. The duration of the obstructions resulting from hernias of all types was a large factor in determining the morbidity and ultimate mortality. This was a more influential factor than the age of the patient or his coexisting physical defects.

4. Delaying operation for the purpose of attempting decompression by intubation of the small intestine in the presence of obstruction due to recognized hernia proved hazardous.

5. Attention was once more directed to the risk of failure to recognize the presence of a hernia in acute intestinal obstruction, and to the danger of en masse reduction by manipulation.

TUMORS

Only slightly less numerous than obstructions due to hernia were those caused by tumor, especially of the large bowel. Naturally the relative incidence of this cause of obstruction was higher in the elderly age group under consideration than in younger patients. This cause must, then, be seriously considered in the diagnosis of acute intestinal obstruction occurring beyond the age of 60.

Our series presented 31 such cases. The average age was 70 years. Distribution of the causative tumors was as follows: sigmoid, 15; rectum, 6; descending colon, 3; hepatic flexure, 2; cecum, 2; lower jejunum, 1; extrinsic tumor, 2 (pelvic recurrences following hysterectomy for carcinoma of the uterus and of

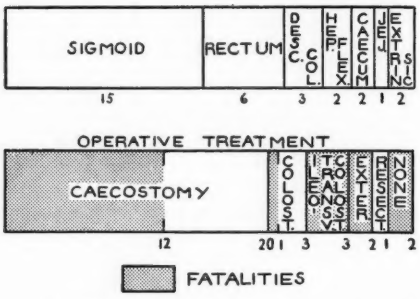

Fig. 3. Distribution of 31 tumors.

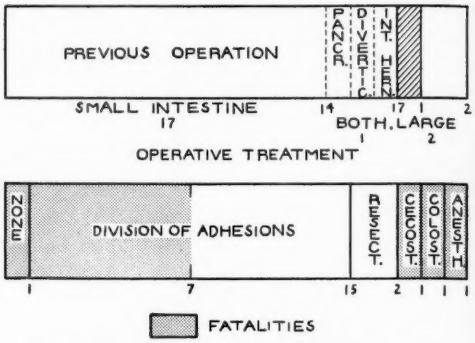

Fig. 4. Etiology and location of adhesions in 20 cases.

the ovary respectively). The tumor was carcinoma in each instance of intrinsic bowel obstruction.

In the obstructions caused by tumor involving the large bowel there was no such direct relationship between the duration of the obstruction and the severity of symptoms as was noted in the case of small bowel obstruction seen in the cases caused by hernia. In general these patients sought surgical relief at a somewhat later time (10). One patient came under observation only after 10 days of obstipation; several of the others after 5 and 7 days. The average duration of symptoms was 3 days.

The delay in undertaking treatment was indicative of the less dramatic and more insidious onset which characterized the establishment of obstruction of the large bowel by tumor. The complete obstipation tended to merge symptomatically with an already existing constipation. There was no sudden pain or peristaltic cramps. Cramps usually developed only after catharsis had proved ineffective. Then followed distention and eventually vomiting, leading at last to discovery of the true situation.

This type of onset was in itself suggestive of the diagnosis, especially when coupled with a history of constipation, melena, and loss of weight. In most instances the diagnosis could be confirmed by rectal examination or by x-ray studies with barium enema.

The preoperative therapy consisted in correcting fluid, salt, and protein deficiencies and the administration of blood when required. In general this preparation was brief, and remedial surgery was promptly undertaken following the introduction of a stomach tube and continuing aspiration.

In one of the hospitals the Miller-Abbott tube was employed in 5 cases as a means of preoperative relief for periods of 12, 8, 4, 3, and 2 days. Four of these patients died following surgery. One of them was found at operation to have developed a perforation of obstructing carcinoma of the cecum.

Anesthetic agents employed for the operations varied as seemed indicated by the patient's condition. Local infiltration anesthesia was frequently used when a simple cecostomy was performed. Less often inhalation anesthesia (cyclopropane or ether), spinal, and pentothal were used. Each served the purpose satisfactorily and there were no accidents attributable to the anesthetic.

The operations varied according to the pathology. Cecostomy was the most frequently used (20 times), being employed for the following tumor obstructions: sigmoid, 12; rectum, 4; descending colon, 2; hepatic flexure, 2. Eight patients survived this procedure for relief of obstruction although 2 of these died following subsequent operations for removal of the obstructing growths. Twelve patients died following the cecostomy alone. Divided colostomy was performed 3 times, with 1 postoperative death. Exteriorization (Mikulicz) was done twice in the presence of acute obstruction, followed by fatalities. Ileotransverse colostomy was done 3 times with 3 deaths. In the single case of obstruction due

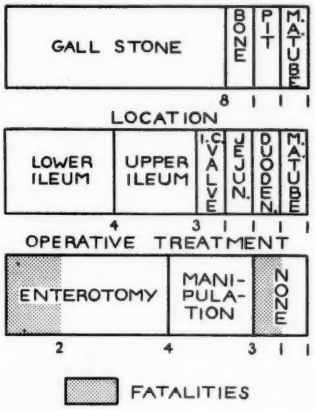

Fig. 5. Type of foreign bodies in 11 cases.

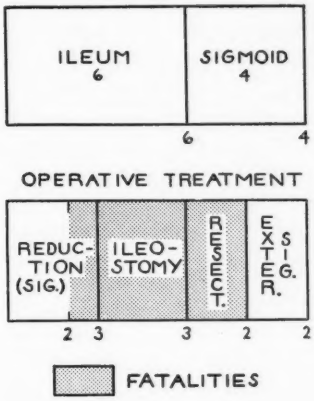

Fig. 6. Location of volvulus in 10 cases.

to carcinoma of the lower jejunum resection and side-to-side anastomosis were carried out. In spite of existing perforation with peritonitis, this patient recovered. One patient was admitted in moribund condition and died without operation.

Postoperative treatment followed conventional lines of support, suction evacuation of stomach and upper intestine, the use of antibiotic medication and ambulation at as early a time as the patient's condition would permit. It was generally observed that the cecostomy or colostomy usually failed to function satisfactorily for the first 48 hours after operation, causing some apprehension as to its effectiveness. Of the complications encountered, pneumonia or atelectasis and renal insufficiency were the most commonly seen. Although the incidence of kidney inadequacy was high, only 1 fatal uremia was seen.

Causes of death among the 18 patients who succumbed shortly after operation for relief of obstruction alone were listed as follows: peritonitis, 6; pneumonia, 5; shock, 4; cardiac failure, 2; uremia, 1. Deaths following later remedial operation (2) were due to peritonitis and shock respectively. Four late deaths were reported, presumably not the immediate result of the obstruction: 1 from coronary embolism (37 days); 2 from pneumonia (17 and 18 days); and 1 from carcinomatosis (21 days). Including these, since they were still under active treatment, and also the 1 fatality not operated upon, gives a record of 22 deaths and 9 survivals, a mortality rate of 71 per cent. The related postoperative mortality was 62 per cent.

From our observations the following impressions were gained:

1. Obstruction due to tumor in this group almost always involved the large bowel and was in each instance caused by intrinsic or extrinsic cancer.

2. The gradual onset of symptoms, merging with previous constipation, led to delay in diagnosis and surgical treatment (5).

3. The prolonged use of upper intestinal intubation did not better the patient's chances of survival (8).

4. Even the simplest measures of surgical decompression were attended by high mortality. Attempts at by-passing operation or extirpation of the tumor in the emergency were almost invariably followed by fatality.

5. Added to the immediate effects of obstruction, the depletion caused by the cancer and the delay in relief led to a very bad prognosis both as to early and late results.

ADHESIONS

Twenty cases of acute obstruction due to adhesions were seen in a group of patients averaging 69 years of age. All but 3 of these patients gave histories of previous operations

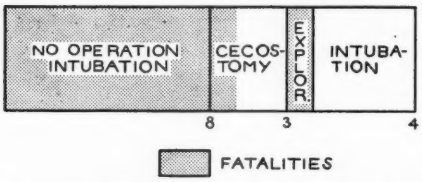

Fig. 7. Undetermined cause of obstruction in 16 cases.

in past years. These earlier procedures represented considerable variety ranging from closure of perforated peptic ulcer to resection of bowel for carcinoma or radium burn. Operations on the appendix and pelvic organs, however, predominated. Of those obstructions from adhesions not due to prior operation, it was interesting to note one which occurred some years after what appeared to have been an acute pancreatitis; another that resulted from a previous diverticulitis of the sigmoid; and a third occurring at the site of protrusion of a loop of ileum through the omentum. Seventeen of the obstructions produced by adhesions were of the small bowel, 2 of the large, and 1 of both.

The symptoms were generally abrupt in onset and severe. They were characterized by crampy pain, early vomiting, obstipation, and distention. The patients were very sick and usually sought medical attention early. The average duration before coming under definitive treatment was 2 days. Of 3 untreated for 5 days, 2 died.

Factors in establishing the diagnosis were the obvious obstructive symptoms and signs, plus the evidence of previous abdominal trauma or inflammation. The x-ray examination was very accurate and helpful in confirming the diagnosis and in differentiating between large and small bowel obstructions (3).

In 15 cases treatment consisted in operation within the first 24 hours after hospitalization, time being given only for necessary replacement and supportive measures and the institution of upper intestinal decompression, usually by Wangensteen's method. Eight recovered and 7 died. Prolonged decompression by Miller-Abbott or Levin tube was pursued in 5 cases. One patient thus treated for 2 days died without operation. Two patients were treated for 6 days and 4 days respectively and died following operation. One treated for 4 days survived after operation. One patient responded to intubation and was relieved by enemas over a period of 6 days and was then operated upon with subsequent recovery. Thus 3 died and 2 recovered following intubation treatment.

Anesthesia used in these operations was predominantly of inhalation type, in the later cases usually with pentothal induction. Cyclopropane was used successfully in 5 cases, ether and nitrous oxide for the remainder. Spinal was used 3 times. One of these spinal anesthesias presented us with the only anesthetic death in the series (and in fact the only such fatality in over 250 operations for emergency surgical conditions in our old age group). This patient vomited during operation, in spite of a stomach tube, aspirated, and promptly died.

Operation in each case revealed the source of the obstruction which, in 15 instances, was relieved by simple division of adhesions. In 1, resection of a loop of ileum was necessary (exteriorization, 2 stage), and the patient survived. One patient with obstruction at the hepatic flexure with gangrene had resection of the bowel with 2 stage ileotransverse colostomy and got well. In 1 case removal of an ovarian cyst was added. The patient died. One with combined large and small bowel obstruction succumbed following cecostomy, as did another following loop colostomy for perforated diverticulitis to which the small intestine was adherent.

The postoperative continuation of suction evacuation of the upper intestine proved most helpful until peristalsis was restored and bowel function re-established.

Of the 20 cases of obstruction from adhesions, 7 patients died during the early postoperative period from the following causes: peritonitis, 2; shock, cardiac failure, pneumonia, uremia, recurrence of obstruction, each 1 case. There were 2 late deaths, 1 from pneumonia (54 days) and 1 from uremia, following transurethral prostatectomy (60 days). Adding these, the one not operated upon, and the single anesthetic death gave a mortality of 11 of 20 cases—a rate of 55 per cent. The related postoperative mortality was 40 per cent.

The following impressions were obtained from observations of acute intestinal obstruction caused by adhesions:

1. A history of earlier abdominal operation or inflammation frequently provided a clue to the cause of obstructions of sudden onset. These lesions usually involved the small intestine.

2. There seemed to be a definite relationship between the mortality and the time elapsing from onset to surgical relief. Generally speaking, the quicker the surgery and the less done, the better the rate of survival.

3. The mortality rate was slightly greater in the patients subjected to preliminary intestinal intubation treatment.

FOREIGN BODIES

A group of obstructions of unusual interest were those produced by foreign bodies in the intestine. There were 11 of these in patients averaging 67 years of age. Eight of the obstructing bodies were gallstones, 1 a peach stone, 1 a meat bone, and 1 a Miller-Abbott tube.

These patients (except the tube case), presenting typical evidences of acute intestinal obstruction with abrupt and dramatic onset, furnished a difficult diagnostic problem. Those who had ingested large foreign bodies had no recollection or gave no history of having done so. Of the 8 gallstone obstructions, only 1 gave evidence of pre-existing gall-bladder disease. X-ray studies, while quite accurate in reflecting the presence of small bowel distention, failed in each instance to show the obstructing agent. The diagnosis was, therefore, highly inaccurate. The difficulty was generally ascribed preoperatively to volvulus or adhesions. In 1 instance a ventral hernia, which was also present, was erroneously taken to be the cause. In another, with early and persistent vomiting following some months of indigestion, an obstructing carcinoma of the stomach was predicted.

These patients came to surgical treatment promptly. Two were operated on within 48 hours of onset, 6 within 24 hours or less. One gallstone obstruction had existed for 7 days. The patient was moribund on admission and died without operation, the obstructing stone

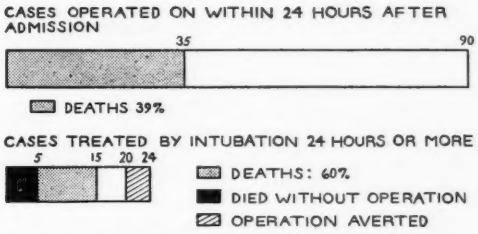

Fig. 8. Effect of intubation treatment on early mortality.

being discovered at autopsy. The patient with obstruction by an ingested meat bone had a 10 day history of acute illness. The obstruction by Miller-Abbott tube was of 2 days' duration.

Operation was performed in all but 2 cases —the moribund patient referred to and the tube case. The obstructing body was discovered at the ileocecal valve once, in lower ileum 4 times, in upper ileum once, in midjejunum once, and in third portion of duodenum once. In 5 instances the intestine had to be opened for removal of the foreign body. Two gallstones were successfully milked out into the cecum and subsequently passed and 1 broke up during manipulation.

Three of these cases merit comment in passing. In the patient who had ingested a meat bone, a large section of spareribs was found to have occluded the ileum, where it had perforated the gut with subsequent spreading peritonitis. The loop was exteriorized and the patient promptly died of sepsis and shock. The patient supposed to have an occluding carcinoma of the stomach was operated on with the recorded intention of performing a rapid anterior gastroenterostomy. The stone was discovered blocking the third portion of the duodenum, and the gut was opened for its removal and resutured. The patient recovered. The third patient had had a colostomy performed as the first stage of a proposed Lockhart-Mummery operation for carcinoma of the rectum. The Miller-Abbott tube, previously introduced, resisted attempts at withdrawal and evidences of small bowel obstruction developed. X-ray examination showed the bowel sharply kinked at the lower ileum with the tube in it, while the small intestine above was greatly distended. The distention

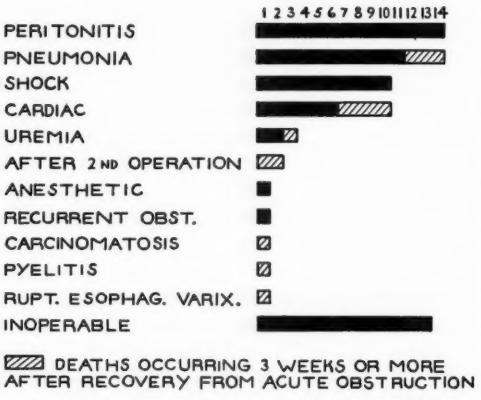

Fig. 9. Causes of death in 123 cases of obstruction.

was relieved by suction with a Levin tube; the Miller-Abbott tube was cut and subsequently discharged through the colostomy.

The results of these procedures were gratifying in all instances in which the bowel was not opened. These 3 patients made uneventful recoveries. Of the 5 in whom bowel opening was required, 3 recovered and 2 died. Thus of the 11 patients coming under observation, 8 recovered and 3 died. The mortality rate was 27 per cent.

The following impressions were obtained from study of these cases:

1. The foreign body obstructions proved to be abrupt, severe, and difficult to diagnose as to etiology. Histories suggesting pre-existing cholecystitis were notably lacking in the gallstone cases (11).

2. Operations for relief, when promptly undertaken, were generally effective. When the release of obstruction did not involve opening the bowel, they were not attended with grave risk even in elderly patients.

VOLVULUS

Ten cases of acute obstruction due to volvulus were recorded. The average age of these patients was 72 years. The areas of gut involved were: ileum, 6; sigmoid, 4. Only 2 gave histories of previous abdominal operations. Duration of obstruction in 5 patients was 1 day or less. Of these, 3 survived operation. Two patients with 3 day old obstructions got well. Two patients with acute symptoms for 4 and 5 days died after surgery.

Diagnosis of volvulus as the cause of obstruction, when correctly made, was arrived at by exclusion, being predicated on the absence of other ascertainable likely causes. Abruptness of onset without premonitory complaint and the severe cramp-like character of the pain were suggestive features. The x-ray examination proved quite accurate in determining whether the obstructive site was in the large or small bowel. One notable error in diagnosis was the designation of a case of volvulus of terminal ileum as acute appendicitis.

With 1 exception, these patients were rapidly prepared by appropriate replenishment therapy and operated upon promptly. In 1 case a Miller-Abbott tube was employed for 2 days without relief, and the patient died following surgery.

Anesthesia employed was: local, 1; spinal, 1; local and cyclopropane, 1; inhalation, 7. All were given without untoward incident.

The operations consisted of: simple reduction of volvulus, 3; resection and anastomosis (ileum), 2; ileostomy, 3; exteriorization of loop (colon, sigmoid), 2.

Two of the 3 patients in whom simple reductions were accomplished recovered. The other (a 4 day case) died of shock within 24 hours postoperatively. In both cases of resection for gangrenous ileum the patients died shortly. Three patients in whom ileostomy was done for ileal volvulus all died. In both cases of exteriorization of large bowel loop (Mikulicz-Paul procedure) the patients survived. Thus there were 6 deaths in 10 patients operated upon, all directly related to the surgical condition. The mortality rate was 60 per cent (11).

The following impressions were obtained from a study of these cases:

1. Volvulus appeared to produce one of the most vicious types of obstruction seen in the older age group. Often resulting in compromise of the bowel's circulation, it led rapidly to gangrenous changes.

2. Efforts at surgical relief, unless undertaken very early, were relatively unsuccessful.

3. Volvulus of the small intestine, occurring somewhat more frequently than that of the

large bowel, proved very much more dangerous. When the ileum required resection or even when ileostomy was chosen as a less formidable procedure, the results were almost uniformly bad.

UNCLASSIFIED OBSTRUCTIONS

In the total number of 123 patients over the age of 60 who were treated for intestinal obstruction, there were 16 the cause of whose difficulty could not be determined. Their average age was 71 years. They are listed as follows: died without operation (no autopsy), 8; palliative operation, pathology not discovered, 3; relieved by nonsurgical measures, 4; surgical exploration, cause not discovered, 1.

The 8 patients who died without operation were either admitted in such bad condition, usually following prolonged obstruction, that operation could not be undertaken (5 cases), or failed to respond to continued intubation procedures (3 cases—4, 2, and 1 days' treatment).

Of 3 patients treated by palliative operation without exploration (cecostomy), 1 was relieved but died on the thirty-fourth day of pyelitis, while 2 survived without subsequent determination of the cause of obstruction. It seems fair to assume that the survivors had probably suffered from volvulus which spontaneously reduced after decompression (1). The same assumption might be made concerning the 4 patients who recovered after intubation and without surgery. In all 4 the evidences of obstruction were of 36 hours' duration or less. The patient who was explored without determining the cause of obstruction died 2 days later.

In this group of unclassified obstructions, 6 patients survived and 10 died. The mortality rate was 62.5 per cent.

From observation of the group the following impressions are presented:

1. This group contained two widely differing types of cases: (a) patients who were virtually moribund when first seen, constituting more than half the number, and on whom no operation could be done effectively; (b) the remainder, who responded fairly promptly to palliative operation or to nonsurgical measures and who subsequently showed no cause for the obstruction and suffered no recurrence of it.

2. Only in this second group (4 cases) among all types of obstruction, did nonsurgical methods of treatment prove of value in safely avoiding operation. This result was, however, entirely unpredictable in the individual case.

GENERAL OBSERVATIONS

Our experience with these patients led to certain impressions which might be briefly summarized:

1. Acute intestinal obstruction in our patients over 60 was an extremely serious accident, carrying a mortality rate of 57 per cent from all causes and of 47 per cent from directly related causes (11).

2. This high mortality was influenced by several factors. These factors had to do fundamentally with the obstruction itself and its treatment rather than with the patient's age and his coexisting ailments:

a. Duration of the obstruction. The longer the condition existed, the poorer the chance of recovery (7).

b. Location of the obstruction. Obstructions involving the small bowel primarily, of whatever nature, were more lethal than those of the large bowel. Their onset was more acute, their deteriorating effect more rapid, and the threat of gangrene greater (5).

c. Nature of the obstruction. Obstructions due to tumor, usually occurring in the large intestine, were habitually discovered quite late and showed a low survival rate. When due to hernia, adhesions, or foreign bodies, the condition was more severe and abrupt in onset. In proved volvulus, perhaps due to more frequent and earlier interference with the blood supply, the overall results were worst.

d. Method of treatment. Delay in furnishing relief of the distention, with or without the need for appropriate disposition of gangrenous gut, added to the hazard. This delay seemed hardly justifiable beyond the time required to empty the stomach and to correct depletion of fluids and electrolytes and, when necessary, to administer blood (2, 8, 5, 9).

Prolonged attempts at intubation increased the delay and did not improve the patient's

chances of survival (5). The mortality among patients operated upon within 24 hours was 39 per cent as contrasted with 60 per cent in those treated by intubation over 24 hours. In only 4 instances of 30 cases in which it was employed as definitive treatment did protracted intubation avert operative intervention, while 5 patients thus treated died without operation. When the cause of the obstruction was recognized, as in hernia, or demonstrated tumor, justification for continued intubation was not easy to establish.

Intubation of the stomach with Wangensteen suction was a necessary preoperative therapy and a most valuable postoperative measure. The Miller-Abbott tube demonstrated its greatest usefulness in the postoperative period (3).

Best results were achieved when the operation performed was the simplest which would relieve obstruction and eliminate the danger of gangrenous gut. Formidable resections and correction of incidental pathology increased mortality when undertaken in the presence of acute obstruction (5).

The use of general anesthesia did not constitute a serious hazard either at operation or in the postoperative course (6). Spinal anesthesia was not satisfactory when employed in this age group.

Supportive treatment, the liberal use of blood and protein hydrolysates, the antibiotics, and early rising proved valuable adjuncts to postoperative recovery. Pneumonia and renal insufficiency were the most troublesome unrelated complications. Kidney dysfunction had frequently to be combatted and was occasionally fatal. Overuse of salt and waterlogging needed to be guarded against (2).

e. Age and condition of patient. These seemed to be factors of secondary importance as compared with the preceding ones. Age and its diseases affected mortality adversely in two ways. First, by diminishing the resistance of the individual to the deteriorating effects of the obstruction. This was an imponderable factor. Second, by providing a fairly constant though low percentage (10 per cent) of late fatalities from conditions not directly attributable to the obstruction or its treatment, but rather to the patient's pre-existing or coexisting ailments.

3. In view of the foregoing findings it is believed that in patients suffering from acute intestinal obstruction old age with its incidental ailments should not serve as a deterrent or as an encouragement to procrastination or palliative measures, but rather as a spur and incentive to the surgeon to undertake prompt and simple operative measures for relief.

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REGENERATION OF THE LIVER IN THE DOG AFTER PARTIAL HEPATECTOMY

Role of the Venous Circulation

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IN a dog, when all of the blood from the portal vein is shunted into the inferior vena cava, the liver becomes smaller and the dog can be maintained only by constant and special care; this has been known and studied for many years. The observation has caused some physicians in recent years to be concerned lest operations which divert all or part of the portal blood into the vena cava, in order to diminish pressure in collateral veins of the portal system in cirrhosis of the liver of man, should have a harmful effect on the liver. If most or all of the blood from the portal system is diverted into the systemic venous system by way of collaterals, a condition which can be brought about in dogs by gradual constriction or occlusion of the portal vein where it enters the liver, the liver becomes smaller. The question, why does alteration of its portal blood supply by these procedures have an adverse effect on the liver of the normal dog, has incited considerable old and new research on the role of the venous circulation of the liver. The present report will describe results of experiments in which the venous circulation to or in the region of the liver was altered and the effects on the liver were judged according to its capacity to regenerate; no such study can be complete, except within its scope, and ours is to be considered only as a step in a program which we are carrying on to learn more about the role of the venous blood supply of the liver.

Earlier studies have already imparted much (1–6). It has been observed that a shunt from the vena cava to the portal vein in which the vena cava and not the portal vein is occluded, a reverse Eck fistula, does not impair the health or affect the liver of a dog. Nor, when the portal vein is occluded at a second operation in such a dog, is the liver affected. Again, resection of part of the liver in a dog with a portacaval shunt will not be followed by an increase in size of the remnant when the portal vein is ligated (true Eck fistula).

This report will describe experiments on dogs in which 70 per cent of the liver was removed and the degree of restoration which followed was estimated. Experiments were performed on normal dogs and on dogs in which either the portal vein or the inferior vena cava or both were constricted at some time in relation to partial hepatectomy.

METHODS

Healthy, adult, mongrel dogs were used in this study. All operations were performed with the usual aseptic technique and with the dog under ether anesthesia, the latter being administered by an insufflation machine in all operations performed through the chest. Partial hepatectomy was performed through an incision in the tenth right interspace and an incision in the diaphragm which extended from the ventral end of the thoracotomy incision to the tendon, and thence along the tendon laterally. The diaphragmatic attachment of the left lobe of the liver was divided, and the two left lobes and the large, bifurcated gallbladder lobe were delivered through the opening in the diaphragm. Each of these lobes was completely removed by clamping and dividing its pedicle. The stump of each pedicle was ligated with one or two heavy, cotton, transfixing ligatures. Fragments of crushed or devitalized liver were removed, and the

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diaphragmatic and thoracotomy incisions were closed. After the gallbladder had been removed, the resected lobes of liver were weighed. The weight in grams was taken to be 70 per cent of the weight of the whole liver before resection because we had found that in similar resections on recently killed dogs with normal livers we removed between 68 and 73 per cent of the liver.

At the time of necropsy the remaining lobes of the liver were removed and weighed. The weight was compared with the calculated weight of liver left after partial hepatectomy, that is, 30 per cent of the calculated weight of the whole liver, or three sevenths of the weight of the resected lobes. When no regeneration occurred, the weight of the remnant at the time of necropsy was approximately the same as the estimated weight of the remnant at operation. Subtraction of the calculated weight of the original remnant from the weight at necropsy gave the number of grams of liver that had regenerated. For convenience, we have expressed the latter figure in terms of percentage, by dividing it by the calculated weight of the original remnant and multiplying by 100.

Constrictions of the inferior vena cava and portal vein were produced by a method that we have described (7) and used in many studies. In the present experiments a strip of laminated cellophane tape was passed twice about the vein and drawn up tightly enough as it was tied to reduce the diameter to a little more than half. The fibrosis which such bands caused led in 2 to 3 weeks to local constriction of the vein to an internal diameter of about 2 to 3 millimeters. In some experiments the vein was completely ligated before or at the time of hepatectomy; such a precaution, however, appeared to be unnecessary because the usual stricture was so great that little or no flow of blood could occur. In 3 experiments we released the stricture on the portal vein before or after partial hepatectomy by removing the cellophane band and dividing the constricting fibrous band.

The technique used for portacaval shunts was the side-to-side anastomosis technique used in this laboratory for many years. In one experiment the shunt was made at the time of hepatectomy through the thoracicoabdominal incision.

At the end of the study the dogs were anesthetized, and a laparotomy was performed. The presence of abnormal development of collateral veins was noted. Pressures in the portal vein and the inferior vena cava were measured by water manometers attached to flexible plastic tubes which had been inserted into these veins through a branch of the splenic or the femoral vein. Zero pressure was based on the anatomic level of the vena cava. The dogs were then killed, and a necropsy was done.

HEPATIC REGENERATION

The gross appearance of the liver at the time of necropsy was distinctly different in experiments in which the calculated gain in weight was relatively large from its appearance in experiments in which the gain was relatively small. In the latter the liver was soft and flabby, the lobes were thin and their edges were sharp, and liver markings were absent on the surface and cut surface. When the gain in weight was considerable, the liver was firm, the lobes were thick and their edges were rounded, and liver markings were conspicuous. The differences did not appear so great at histologic examination as grossly. All of the livers appeared quite normal. However, the sinusoids were slightly wider and contained more blood and the parenchymal cells were slightly larger in sections taken from the livers which had regenerated to a significant degree as compared to normal livers or the livers which showed little regeneration.

Some degree of regeneration, as was manifested by the difference between the number of grams that the liver weighed at the time of death and its calculated weight at the time of partial hepatectomy, was shown by all dogs which survived longer than a few days.

Normal dogs (9 dogs). All of the normal dogs survived partial hepatectomy and recovered quickly from the operation. At the time of necropsy, 30 to 42 days after operation, they were at their preoperative weight and in excellent condition. The livers of all the dogs showed a marked degree of regeneration, the mean regeneration for the group being 233 per cent (S.E. ±23) (Table I).

TABLE I.—REGENERATION AFTER PARTIAL HEPATECTOMY (70 PER CENT)

Conditions	Dogs	Body weight, kgm.	Liver removed, gm.	Days between hepatectomy and necropsy	Liver weight at necropsy, gm.	Per cent regeneration*	Per cent of original weight at necropsy†
Normal	9	10±1‡	183±10	30–42	260±20	233±23	100
Reverse Eck fistula	3	13±1	246±15	30–60	323±25	212±24	92
Portal vein occluded							
Only constriction of portal vein	6	7±1	116±17	30–105	72±9	47±12	42
+Constriction released	3	10±1	185±30	35–75	177±12	133±33	67
+Caval constriction	6	12±2	196±14	31–120	181±32	126±23	65
+Caval constriction later	3	9±1	130±23	30–71	148±6	181±53	80
+Thoracic inferior caval constriction	2	14	193	75–80	240	184	87
+Reverse Eck fistula	2	16	297	30–35	275	124	65

*233 per cent regeneration—original liver weight.
†30 per cent of original weight at necropsy—no regeneration.
‡The figures after ± represent the standard error of the mean.

Pressure in the inferior vena cava and the portal vein was measured in 7 of the 9 dogs (Table II) at intervals of about 1 week and 2 weeks after operation, and just before necropsy. At 1 week internal portal pressure was greater than normal, being 18 to 21 centimeters of water, and caval pressure also was greater than normal, being 7 to 9 centimeters of water. A month after partial hepatectomy portal and caval pressures had decreased to nearly normal levels, 12 to 15 centimeters for the portal pressure and 3 to 5 centimeters for the caval pressure. In 3 dogs there appeared to be slight engorgement of the portal veins; the others had no engorgement, and in none had portal collateral veins developed.

Reverse Eck fistula (3 dogs). The dogs with reverse Eck fistulas, a portacaval anastomosis with ligation of the vena cava between the anastomosis and the liver, were like normal dogs in that they were in excellent general condition at the time of necropsy 30 to 60 days after partial hepatectomy. The reverse Eck fistula was made 2½ months before hepatectomy in 2 dogs in which the regeneration was 175 per cent and 205 per cent respectively. The reverse Eck fistula was made at the time of partial hepatectomy in the other dog; regeneration of the liver was 256 per cent.

Portal and caval pressures taken before necropsy were about the same for each dog; the lowest pressure was 13 centimeters (both vessels) and the highest was 18 centimeters of water. There was only slight engorgement of the portal system and a slight degree of development of portal collateral circulation in these dogs. On the other hand, development of caval collateral circulation, as manifested by large, tortuous veins in the abdominal wall, was marked.

Portal constriction (6 dogs). After hepatectomy all the dogs with constriction of the portal vein did very poorly. There were 16 dogs in this group but only 6 lived longer than a week. Of the other 10 dogs, 1 died in a week and 9 died within the first 3 days. At the time of operation, when partial hepatectomy was

TABLE II.—VENOUS PRESSURES (CM. OF WATER)

Venous alterations	Liver unaltered*		After partial hepatectomy	
	Inferior vena cava	Portal vein	Inferior vena cava	Portal vein
Normal dogs	−2 to +3	7 to 11	9 to 3†	21 to 12†
Reverse Eck fistula	5 to 20	3 to 12	13 to 18	13 to 18
Portal vein occluded				
Only constriction of portal vein	−2 to +2	8 to 11	1 to 2	8 to 13
+Constriction released			4 to 5	18 to 19
+Caval constriction	4 to 18	9 to 22	8 to 19	15 to 22
+Thoracic inferior caval constriction	9 to 15	12 to 20	10	15
+Reverse Eck fistula	7 to 11	6 to 16	13 to 18	13 to 22

*From Volwiler and associates (7).
†In normal dogs the higher figure is the one obtained at 1 or 2 weeks after partial hepatectomy. The lower figure was obtained 4 to 5 weeks after partial hepatectomy. In other groups the pressures were taken before necropsy.

performed, the livers of these dogs appeared small. The lobes were thin, and the edges were sharp. The body weight was slightly less at the time of partial hepatectomy than it had been several months before when the cellophane band was applied to the portal vein, and it was considerably less at the time of necropsy. Of the 6 dogs which survived partial hepatectomy and lived at least 30 days 2 died and 2 were moribund when killed.

The regeneration of the liver in the group of 6 dogs was low, the mean being 47 per cent (S.E.± 12). The greatest degree of regeneration (81 per cent) was in a dog maintained for 105 days. Yet this dog, like the others, failed slowly and was in poor condition when killed.

Venous pressures could be determined in only 2 of the 6 dogs, and both of these dogs were thin, weak and anemic, and required very little anesthetic. In both the caval pressure was 1.5 centimeters of water while portal pressures were 7.5 centimeters and 13.3 centimeters. Marked engorgement of the portal system and marked development of portal collateral circulation were noted in all the dogs of this group at the time of partial hepatectomy and at necropsy. The inferior caval system appeared normal.

Constriction of portal vein released (3 dogs). Removal of the cellophane band and division of the fibrous band constricting the portal vein were performed in 1 dog 2 months before partial hepatectomy and in 2 dogs 1 month after hepatectomy. All 3 dogs gained weight after the stricture was released. The dog in which release had been performed before partial hepatectomy had a normal-appearing liver at the time of hepatectomy; and at the time of necropsy, 35 days later, it had 196 per cent regeneration of the remnant of the liver. The other 2 dogs were almost moribund when their portal strictures were released, and their remnants of liver then showed no signs of regeneration. Thereafter they gained weight and improved generally rapidly. One of these, killed 75 days after partial hepatectomy, had 87 per cent regeneration of liver; and the other, killed 60 days after hepatectomy, had 115 per cent regeneration.

The portal pressure of these 3 dogs just before necropsy was 18 to 19 centimeters of water, and the caval pressure was 4 to 5 centimeters. Collateral circulation and engorgement of the portal system, which were observed at the time of partial hepatectomy, did not disappear and were present at the time of necropsy. Caval engorgement and prominent veins of the anterior abdominal wall were found at necropsy in only 1 dog, a dog in which the principal region of regeneration was the caudate lobe and process, and in which the liver surrounded and compressed the vena cava.

Portal and caval constriction (6 dogs). The general condition was good and the liver appeared quite normal at the time of partial hepatectomy in the 6 dogs with constriction of both the portal vein and the vena cava. All the dogs survived hepatectomy, and only 1 was in poor condition when it was killed. The mean regeneration of liver was 126 per cent (S.E.± 23). Complete or nearly complete stricture of the vena cava and the portal vein was present in 3 of the 6 dogs; in 1, killed at 31 days, regeneration was 113 per cent; and in 2 dogs, killed at 120 days, regeneration was 190 per cent and 204 per cent. In the other 3 dogs, including the one in poor general condition, constriction of the portal vein was marked, but the diameter of the vena cava at the point of constriction was 5 millimeters in 2 dogs and only slightly reduced in the other.

The differential between portal and caval pressure was less than normal in this group of dogs, pressures in the portal vein being 15 to 22 centimeters of water (average, 17.2 cm.) and in the vena cava 8 to 19 centimeters (average, 13.0). Portal congestion and collateral development were marked. Congestion of the inferior caval system and collateral circulation in the abdominal wall were marked in the 3 dogs with the greatest constriction of the vena cava, but less marked in the others.

Portal constriction, caval constriction later (3 dogs). In 2 dogs which had constrictions of the portal vein, cellophane bands were placed around the vena cava just caudal to the liver at the time of partial hepatectomy. Both survived and were in good condition when they were killed. A band was placed on the third dog 1 month after partial hepatectomy, when the dog was in such poor condition that it was

doubtful whether it would survive administration of an anesthetic. However, the dog survived, began to improve, and was in good condition when killed 71 days after partial hepatectomy. The mean regeneration of these dogs was 181 per cent (S.E.± 53).

Portal and caval pressures, engorgement of veins and development of collateral circulation were the same in these dogs as in those in which both the portal vein and the vena cava had been constricted before hepatectomy.

Portal constriction, thoracic inferior caval constriction later (2 dogs). One month after partial hepatectomy had been performed in 2 dogs which had constrictions of their portal veins, at a time when the dogs were in poor general condition, cellophane bands were applied around the vena cava just above the diaphragm. Until abdominal ascites began to develop, shortly before these dogs were killed 75 to 80 days after hepatectomy, they improved steadily. Liver regeneration was 158 per cent for 1 dog and 210 per cent for the other. The livers of both dogs, although they appeared congested, showed the usual signs of hypertrophy. The abdomens of both dogs were moderately distended by clear, faintly yellow fluid.

About the same degree of venous engorgement, collateral development and approximately the same portal and caval pressures were seen as in dogs with constrictions of the portal vein and the vena cava below the liver.

Reverse Eck fistula and ligation of portal vein (2 dogs). Before partial hepatectomy 2 dogs with reverse Eck fistulas (portacaval anastomosis and ligation of the vena cava above the shunt) underwent ligation of the portal vein between the shunt and the liver. These dogs were in good condition when they were killed 30 and 35 days after hepatectomy, and hepatic regeneration was 103 per cent and 144 per cent, respectively. Pressure, venous engorgement, and collateral development were about the same as in the dogs with reverse Eck fistulas but with no obstruction of the portal vein.

COMMENT

From this experimental study it would appear, firstly, that the liver of the dog will not regenerate to a very great extent if the portal vein alone is obstructed, and secondly, that good regeneration will occur if the inferior vena cava is obstructed, even when the portal vein is also obstructed. The reasons for the difference in the capacity of the liver for regeneration in the presence of portal obstruction, according to whether or not there is obstruction of the inferior vena cava, are not known and can be learned only by further study. It might be postulated that the liver needs to be well filled with venous blood for good regeneration to occur after partial hepatectomy, and that, when filling from the portal vein route is greatly restricted, any procedure which will produce filling of the hepatic veins will favor regeneration of the liver. If this postulation should be correct it is easy to see that a constriction of the vena cava above the liver will distend hepatic veins, but less easy to understand how constriction of the vena cava below the liver could have such an effect unless one makes a second postulation, one such as has been used to explain the difference in the livers of dogs with true Eck fistulas and dogs with reverse Eck fistulas and ligated portal veins. In the latter, occlusion of the vena cava below the liver makes the thoracic vena cava a vessel which carries blood only from the liver. Rhythmic stasis, or even reverse flow, which might occur in the thoracic inferior vena cava during the respiratory cycle, might be reflected in hepatic veins.

In an earlier study (7) we had observed that when only the portal vein was obstructed the liver seemed to shrink in size, and that when both the inferior vena cava below the liver and the portal vein were obstructed the liver did not appear to shrink. The present study makes it clear that this difference is reflected in the disparate capacity of the liver to regenerate in the two conditions. The study also brings out more emphatically the difference that we had observed in the general physical condition, the poor condition of dogs with obstructions of the portal vein alone, as contrasted to the good condition of dogs with obstruction of both the portal vein and the inferior vena cava. We have found that the latter dogs appear to be in as good condition 2 years after the two vessels have been obstructed as they were before obstruction.

The experiments in which improvement of general condition and restoration of livers were brought about, in dogs with simple portal obstruction, by another procedure were of two types. In one, release of the constriction of the portal vein was effective. In the other, a stricture of the vena cava was added to a stricture of the portal vein. The results we have obtained after release of the portal stricture support the hypothesis that venous filling of the liver encourages restoration after partial hepatectomy, and our results after constriction of the inferior vena cava support the hypothesis that distention of the hepatic veins might compensate in part for restriction of portal venous supply.

Generally, portal and caval pressures in this study were a reflection of obstruction, being high in either vessel when obstruction existed. There were, however, several exceptions to this generalization. After a portal stricture was released, portal pressure remained above normal, and collateral veins did not shrink appreciably. This finding should be studied further and over a longer period. Again, although it is not surprising that portal pressure was above normal for a while after partial hepatectomy and that the pressure declined as restoration of liver and of the portal bed occurred, it is surprising that caval pressure was high and fell concomitantly. Certainly, partial obstruction of the vena cava by a mass of regenerated liver was not the causative factor, or the pressure would not have fallen. The third apparent exception is probably not a real exception. That is, the finding of a normal portal pressure after partial hepatectomy in the 2 dogs with obstruction of the portal vein in which measurement was possible indicates, more likely, the debilitated condition of these dogs.

SUMMARY

In dogs, the liver becomes considerably smaller when the portal vein is occluded whether or not a portacaval anastomosis is made. To study this phenomenon we have performed standard (70 per cent) hepatectomy in normal dogs and in dogs with various types of obstruction of the portal vein and the vena cava, and have compared degree of regeneration of the liver as well as pressure and collateral development in the inferior caval and portal systems.

Very little regeneration occurred in dogs with occlusion or severe constriction of the portal vein, and the general condition of these dogs declined rapidly. However, release of the portal stricture or obstruction of the vena cava either below or above the liver resulted in much greater degrees of hepatic regeneration and general improvement in such dogs.

Marked hepatic regeneration occurred in normal dogs, and almost as great degrees of regeneration were found in dogs having portacaval shunts and ligated venae cavae above the shunts. Good regeneration was observed in dogs with constriction of both the portal vein and the inferior vena cava below the liver, and in dogs with a portacaval shunt and ligation of both the vena cava and the portal vein.

Inferior caval pressure and portal pressure were above normal a short while after partial hepatectomy in normal dogs. Portal pressure was high and portal engorgement and collateral development were marked in the portal system of dogs with constriction or obstruction of the portal vein, even in those dogs in which the stricture had been relieved.

Caval pressure was high and collateral development was marked under all circumstances in which the vena cava was constricted or ligated. Caval pressure was the same as the portal pressure in experiments in which there was a portacaval shunt.

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STUDIES ON FLASH BURNS: THE PROTECTIVE EFFECTS OF CERTAIN FABRICS

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CLINICAL studies of flash burns emphasized that these burns were largely confined to exposed skin areas and that clothing afforded a high degree of protection against burning. In reporting the Pearl Harbor experience, Eckert and Mader wrote: "Only exposed surfaces were burned; even an undershirt or shorts appeared sufficient to protect the areas covered from being burned." Reports from Hiroshima and Nagasaki indicated that, although most flash burns were confined to exposed areas, a few cases were seen in which burning occurred through one or more layers of clothing (6). It was also noted that dark clothing, which has a low radiant energy reflectance, afforded less protection than white clothing. Further clinical observations (5) indicated that clothing wet with perspiration and adherent to the skin might have been responsible for some of the burns on covered areas.

A more precise knowledge of the protection afforded by clothing was desirable. The present experiments were designed to study the skin burns produced by a brief exposure to high intensity radiant energy when the skin was covered by certain fabrics and fabric combinations. The changes in protection due to dyeing and to moistening some of the fabrics were also tested.

MATERIALS AND METHODS

This work was carried out with the carbon arc searchlight described in the threshold burn studies previously reported (3). A similar group of Chester White pigs was used, and their preburn and postburn treatment was identical in the two studies. In some cases the same animals were used in both experiments.

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The fabric or combination to be tested was attached to the inner surface of the perforated transite shield and the animal positioned in gentle apposition to it. All experiments were done with a 1 second exposure and with variations in the incident energy so that the results would be directly comparable with those obtained in the threshold studies on unprotected skin.

The fabrics studied were herringbone twill cotton, linen, water-repellent sateen, wool serge, silk, and two batches of cotton undershirt fabric. Herringbone twill was a rough fabric of greenish-brown color. It had a relatively porous weave and showed moderate transmission of a flashlight beam when the light was held directly against the material. The linen had a rough texture, a slightly irregular surface, and a light yellow color. Its weave was quite porous, and a flashlight beam was readily transmitted. Sateen was a greenish-brown fabric with a smooth, slightly shiny surface. It was closely woven and transmitted a flashlight beam poorly. Serge was a rough, heavy material of olive drab color. Its weave and light transmission were essentially like that of sateen. Silk was a thin, shiny white material with a slightly irregular surface. Although it was closely woven, this material was thin enough to transmit light about as well as linen. The two batches of cotton undershirt fabric were of similar appearance. Both were thin, white, loosely knit materials which transmitted light about as readily as linen or silk. In certain experiments batch A of undershirt material was dyed black. Dyeing this material decreased its light transmission slightly.

Light transmission was also measured by using an Ansco-Sweet densitometer. Densitometer readings for single layers of the fabrics were as follows:

	Dry	Wet
Herringbone twill	2.65	2.72
Linen	0.95	
Sateen	3.0 *	3.0
Serge	3.0	3.0
Silk	0.81	
Undershirt A	0.76	0.73
Undershirt B	0.79	
Undershirt A black	1.42	1.54

*Note: 3.0 was the limit of the instrument used.

These measurements confirmed the visual impression gained with the flashlight beam.

The two undershirt materials were tested in combination with the other fabrics. In the cloth combinations, the two layers were placed together in front of the animal with the undershirt material against the pig's skin. Herringbone twill, sateen, and serge were tested in combination with batch A, and silk and linen with batch B. In another study using batch B, the fabrics were reversed and herringbone twill was placed against the animal's skin with the undershirt material outside. Also, a series of experiments was done using two layers of undershirt material, batch B, in front of the animal.

Herringbone twill, sateen, serge, batch A of undershirt material, and black undershirt material were also tested after being moistened. The fabric was allowed to stand in tap water until thoroughly soaked. It was then removed from the water and any excess moisture removed by gentle blotting with a paper towel. The fabric was then placed in front of the animal and the exposure carried out immediately before further drying could occur. In several experiments normal saline was substituted for tap water without altering the results.

In these studies a series of 5 to 10 burns was produced in each experiment. The total number of burns, experiments, and animals used in each group is shown in Table I.

TABLE I.—FABRICS AND FABRIC COMBINATIONS TESTED

Material	No. of burns	No. of experiments	No. of animals
Herringbone twill	39	6	6
Sateen	47	7	6
Serge	61	9	7
Linen	47	6	4
Silk	47	6	5
Undershirt material, batch A	87	14	10
Undershirt material, batch A black	48	6	5
Undershirt material, batch B	30	4	4
Herringbone twill and undershirt material A	60	8	7
Sateen and undershirt material A	57	8	7
Serge and undershirt material A	63	8	6
Linen and undershirt material B	50	6	6
Silk and undershirt material B	48	6	5
Undershirt material B, two layers	46	6	6
Undershirt material B and herringbone twill	53	6	4
Herringbone twill wet	63	8	8
Sateen wet	62	8	8
Serge wet	58	10	9
Undershirt material A, wet	43	6	6
Undershirt material A, black wet	48	6	5

RESULTS

The grading system described in the threshold studies (3) was also used in these experiments. A 0 response indicated no damage on gross examination at 24 hours. Erythema alone at 24 hours was labelled 1+. Burns with central or patchy surface coagulation were called 2+, and burns completely covered with coagulation were labelled 3+. In the threshold studies a 4+ burn showing carbonization was also recognized. In the present studies, however, no attempt was made to distinguish a 4+ from a 3+ lesion. When fabrics were charred through and adherent to the skin, it was difficult or impossible to know if the skin was carbonized. Also, with the darker fabrics, dye transfer occurred at the higher intensities, giving a brown color to the coagulum in the absence of carbonization. Consequently, all burns greater than 2+ were termed 3+ in the present study. The clinical course of these lesions was observed and appeared to be identical with lesions of similar grade on unprotected skin.

The results of these experiments are listed in Table II. Effects noted on fabrics as well as on the skin are shown. A detailed tabulation of the data on which this table is based has been published in a preliminary report elsewhere (4). As mentioned, dye transfer to the animal's skin was regularly noted when

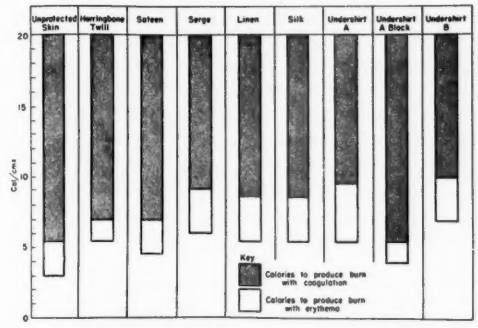

Fig. 1. Protection afforded by single layers of the fabrics. Exposures of energies in the dark area of the bar produced burns with coagulation (2+ or greater); to energies in the lighter area of the bar, burns with erythema (1+); to energies below the bar, no burn.

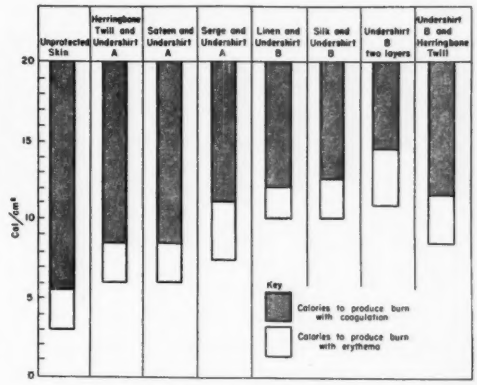

Fig. 2. Protection afforded by fabric combinations. See legend for Figure 1.

the darker fabrics (herringbone twill, sateen, serge, undershirt material dyed black) were exposed to the higher intensities. However, dye transfer did not occur when these same materials were exposed while wet, but cutaneous damage occurred none the less. The results in all experiments were reasonably consistent except those obtained by using herringbone twill and sateen with undershirt material. In both instances the amount of protection afforded was less in late experiments than in earlier ones. Apparently the fabrics themselves altered somewhat in the course of several months although there was no obvious change.

Figures 1 to 3 show the calories necessary to produce 1+ and 2+ burns in the various experiments, as compared with the threshold values for unprotected skin (3).

DISCUSSION

The caloric values listed in Table II indicate the energy incident on the surface of the fabric. By using these values, a direct comparison can be made between burns behind fabric and burns on unprotected skin. No measurements were made of the calories transmitted through the fabrics to the skin. These figures are of interest and will be measured in future studies.

It was discovered that the effects of the radiant energy on fabrics were not a good indication of what was happening to the skin behind them. In every experiment there were skin burns produced when there was no obvious damage on the surface of the fabric next to the animal's skin. In many cases severe burns with skin coagulation occurred although no damage was visible on either surface of the cloth.

Using as standards the values of 3 and 5.5 calories per square centimeter to produce 1+ and 2+ burns respectively on unprotected skin (3), the calories of protection afforded by the various fabrics and fabric combinations are recorded in Table III. Among the single layers of dry fabric, batch B of undershirt material afforded the greatest amount of protection despite the fact that the fabric transmitted light well. Two layers of this same material proved the most effective combination.

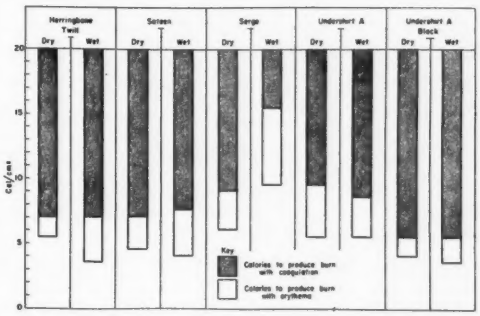

Fig. 3. Protection afforded by dry and wet fabrics. See legend for Figure 1.

TABLE II.—THRESHOLD RADIANT ENERGY REQUIRED TO PRODUCE SKIN BURNS BEHIND FABRICS AND TO PRODUCE FABRIC DAMAGE

Fabric	Threshold cal./cm.² needed to produce		Minimal cal./cm.² needed for fabric damage	
	1+ burn	2+ burn	Arc surface	Animal surface
Herringbone twill	5.5	7	7	10.5
Sateen	4.5	7	5.5	10.5
Serge	6	9	5.5	15.5
Linen	5.5	8.5	10.5	11.5
Silk	5.5	8.5	10	11
Undershirt material, batch A	5.5	9.5	12.5	>15.5
Undershirt material, batch A black	4	5.5	4	5.5
Undershirt material, batch B	7	10	14	>14
Herringbone twill and undershirt material A	6	8.5	5.5	8
Sateen and undershirt material A	6	8.5	7	8.5
Serge and undershirt material A	7.5	11	5.5	15
Linen and undershirt material B	10	12	10.5	13
Silk and undershirt material B	10	12.5	9.5	13
Undershirt material B, two layers	11	14.5	14.5	>15.5
Undershirt material B and herringbone twill	8.5	11.5	13	>15.5
Herringbone twill wet	3.5	7	>11	>11
Sateen wet	4	7.5	15.5	>15.5
Serge wet	9.5	15.5	>18	>18
Undershirt material A, wet	5.5	8.5	>11	>11
Undershirt material A, black wet	3.5	5.5	11	>11

Notes: Values are based on a 1 second exposure in all cases. When a figure is preceded by the symbol (>), exposures at higher levels were not carried out, but the recorded value produced no fabric damage.

TABLE III.—AMOUNT OF PROTECTION AFFORDED BY VARIOUS FABRICS AND FABRIC COMBINATIONS

Fabric	Calories of protection compared to unprotected skin:	
	1+ burn	2+ burn
Herringbone twill	2.5	1.5
Sateen	1.5	1.5
Serge	3	3.5
Linen	2.5	3
Silk	2.5	3
Undershirt material, batch A	2.5	4
Undershirt material, batch A black	1	0
Undershirt material, batch B	4	4.5
Herringbone twill and undershirt material A	3	3
Sateen and undershirt material A	3	3
Serge and undershirt material A	4.5	5.5
Linen and undershirt material B	7	6.5
Silk and undershirt material B	7	7
Undershirt material B, two layers	8	9
Undershirt material B and herringbone twill	5.5	6
Herringbone twill wet	0.5	1.5
Sateen wet	1	2
Serge wet	6.5	10
Undershirt material A, wet	2.5	3
Undershirt material A, black wet	0.5	0

Note: Using a 1 second exposure, threshold values on unprotected skin are 3 cal./cm.² to produce a 1+ burn and 5.5 cal./cm.² to produce a 2+ burn (3).

The studies with white and black undershirt material afforded a demonstration of the importance of fabric color as it influenced skin protection. The white fabric gave about 1.5 calories per square centimeter more protection from erythema and 4 calories per square centimeter from coagulation than did the same cloth dyed black.

When two layers of cloth were used, the protection afforded (Table III) was not necessarily additive. In this respect there was a difference between dark and light fabrics in combination with the undershirt material. Using linen or silk in combination or two layers of undershirt material, the experimental results were in close agreement with those predicted by adding the amount of protection afforded by each of the two layers. When herringbone twill, sateen, or serge was used in front of undershirt material, however, the protection afforded was less than the predicted value in each case. Actually, the combination with either herringbone twill or sateen afforded less protection from coagulation than did a single layer of undershirt material alone. In the reversed experiment, however, when undershirt material was placed in front of herringbone twill, exactly additive protection was found. It would seem that when a dark fabric was exposed to radiant energy, a significant amount of absorption and reradiation or conduction of heat through the undershirt material to the skin occurred. With the lighter colored fabrics, absorption of energy was less marked and the second layer did appear to afford additive protection.

During the course of these studies, two lots of undershirt material were used. They were the same material obtained from the same source and the two lots were identical in appearance. However, there was a consistent difference in the degree of protection afforded, batch B giving greater protection than batch A. The reason for this difference was not apparent but was borne out by simultaneous experiments with the two materials on the same animal.

The studies with wet fabrics showed considerable variation which depended to some extent upon the amount of moisture absorbed by the material. Serge had the greatest water-absorbing capacity of the materials tested and was considerably more protective wet than dry. The other fabrics absorbed a smaller amount of moisture and results differed little between the wet and dry state. Herringbone twill and undershirt material were somewhat less protective wet than dry. Both of these fabrics were darker in color in the wet state and this fact may have been responsible for the decreased protection. It was of interest that all the fabrics were much more resistant to damage in the wet state, but this change was not paralleled by a rise in skin protection.

In these experiments all fabrics were positioned in immediate apposition with the animal's skin. It was recognized that such close positioning was a somewhat artificial condition which occurred infrequently with actual clothing. In future studies, the fabrics will be tested when placed at varying distances from the animal.

In analyzing the different degrees of protection given by the various fabrics, it seemed that the color was of greater importance than their weave, weight, or light transmission. Serge, the heaviest material tested, was the only one of the darker materials affording as much protection from coagulation as the lighter colored fabrics. Sateen, the material with the lowest light transmission, gave very little protection.

Moritz and Henriques concluded from their studies that when animals were exposed to flame temperatures over 1,000 degrees C., "the interposition of anything capable of impeding heat transfer to the skin may be sufficient to make the difference between burning and absence thereof." In the present study, all materials afforded some protection to the skin but the degree of protection was not marked in many instances. Apparently thermal radiation is so intense that a greater barrier to heat transfer is needed to prevent skin damage.

SUMMARY AND CONCLUSIONS

1. Studies of the effects of various fabrics and fabric combinations in protecting the skin of the anesthetized Chester White pig from flash burning were carried out.

2. The effects of changing the color and of moistening certain of the fabrics were also tested.

3. All fabrics afforded some protection but there was considerable variation in the extent of protection with different materials.

4. It seemed that the color of the fabric was the single most important quality in determining the amount of skin protection. Light-colored fabrics were more protective than darker ones.

5. The effect on the fabric itself was not a good indication of the changes in the animal's skin. In all experiments, burns occurred when there was no apparent damage to the surface of the material touching the animal.

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EDITORIALS

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THE IMPORTANCE OF THE ESOPHAGOGASTRIC VALVE MECHANISM IN SURGERY OF THE STOMACH AND ESOPHAGUS

REGURGITATION of intestinal juices into the esophagus following surgery may create a problem as serious to the patient as the original disease. In the enthusiasm of accomplishing formidable operations, hitherto considered too dangerous to use frequently, surgeons have often failed to consider the potential consequences of their efforts. The damaging results of esophageal reflux are more apparent following surgery for benign conditions, such as achalasia or esophageal varices, than for malignant lesions. This is probably true because these patients live longer, but if we wish to advocate radical surgery for cancer of the esophagus and stomach on the basis of greater curability, then we must reduce the high morbidity rate which follows these operations. Refinements in operative technique should eventually accomplish this result. The esophagus is extremely susceptible to the erosive action of acid pepsin juices but it is also susceptible to a lesser degree to intestinal juices. The persistent bathing of this tube with these fluids may lead to esophagitis, erosions, ulcerations, hemorrhages, stenosis and a short esophagus. While this sequence of events may take place, it should be pointed out that there is a distinct variation in esophageal reaction to digestive juices. The reason is not known but may be related to a deficiency state. Individuals have been known to ruminate for years without developing esophagitis.

The symptoms presented by a patient suffering from esophagitis are usually those of heartburn, substernal pain, gastric flatulence and partial regurgitation on lying down or bending over. An incompetent valve mechanism can be demonstrated by gastric pressure during roentgen examination in the Trendelenburg position. Esophagoscopy will demonstrate the presence of esophagitis, erosion, or ulceration.

Many operations on this region have been hurriedly reported as successful but, with the passage of time, multitudinous complaints, usually due to esophagitis, have arisen to plague the surgeon. British physicians have been foremost in pointing out the failure of plastic procedures which produce an incompetent valve mechanism in the treatment of achalasia or cardiospasm. Barrett and Franklin in 1949, reported 16 out of 19 cases showing definite evidence of esophagitis upon prolonged follow-up. Allison of Leeds has corroborated these findings and now many American surgeons are reporting their failure. Time has a habit of

disappointing early enthusiasms for new gastric operations.

The valvular mechanism which prevents regurgitation into the esophagus is not too well known but the major factors can be identified. Lerche in his "Anatomical Studies" has shown that there is an inferior constrictor of the esophagus and a cardiac sphincter resulting from the purse-string effect of the oblique gastric muscles about the lower end of the esophagus. Separating these is the gastroesophageal vestibule. These muscles must play a partial role in regulating the flow of food into the stomach and in closing the esophagus to regurgitation, but do not seem to be sufficiently strong to be independently important as a water-type seal. The intermittent inspirational pinch-cock mechanism of the diaphragm can be observed at esophagoscopy. In addition the contraction of the right crux of the diaphragm pulls down and increases the angle the esophagus makes with the stomach. This action probably prevents the negative pressure in the chest during inspiration from sucking juices into the esophagus. The left-hand turn which the esophagus makes when it emerges from the hiatal sling of the diaphragm may be likened to the effective action of the levator ani on rectal control. Probably the strongest valve mechanism is the angle made by the 1 to 3 centimeters of abdominal esophagus as it enters the stomach. The importance of the angle of entrance can be appreciated if one attempts to perform esophagoscopy through the stomach; it is almost impossible to do so unless traction is made on the lesser curvature. The pressure effect produced by the air bubble of the stomach on the terminal left side of the esophagus as it joins the upward curve of the stomach should have a flap valve effect. The interdigitation of the cardiac rugae lubricated by the mucus glands of the lower esophagus and subject to the action of the underlying muscularis mucosa completes the complex components of Nature's marvelous stopcock. Allison recently emphasized the importance of the elastic esophagophrenic ligament in preserving the permanent relationship of this valve mechanism. Weakening of this ligament and the diaphragmatic muscles, along with the longitudinal contraction of the esophagus, allows the cardia to slide into the mediastinum, destroying the angle which the gullet normally makes with the stomach and opening the way to the possibility of regurgitation.

The application of our present knowledge of valve control is well illustrated in the conservative and operative management of achalasia of the esophagus. Allison believes that the successful results of forcible stretching of the narrowed segment is due to submucosal rupture of the circular muscle fibers, leaving the other factors which prevent regurgitation intact. If dilatation fails to give relief and the symptoms warrant surgical intervention, the modified Heller operation of an adequate vertical incision through the constricted muscles down to the mucosa gives the best promises of doing the greatest good with the least harm. Both Barrett and Allison report a very high percentage of symptomatic relief without the complication of esophagitis. However their cases are still too few and too recent for final assessment. The one danger encountered from this operation is perforation of the mucosa which should be recognized at the time and sutured.

Allison's contribution to the repair of sliding esophageal hernia appears to be important. This is the type in which the stomach is pulled into the mediastinum along with apparent foreshortening of the esoph-

agus, thus producing a dumbbell-like effect with impairment of the valve mechanism. The primary indication for repair is the presence of esophagitis or ulcerations as diagnosed by symptoms, esophagoscopy, and roentgen examination, and the failure of medical management. The latter consists of ulcer diet and medication, dilatation when necessary, and sleeping in the Fowler position. In children and in the aged this management should be continued until severe symptoms justify surgical attack. In good risk patients, surgery should be given earlier consideration if ulceration and fibrosis of the esophagus are to be avoided. In repairing the sliding type of hernia Allison sutures the esophagophrenic ligament to the undersurface of the diaphragm. The hiatal defect is repaired posteriorly thus restoring the normal anatomical relationships. This new technique appears to be important though its permanent place in modern surgery must await the evolution of time. It is a simple procedure and at best can do no harm. If the success of this operation is demonstrated the advocates of the abdominal approach will lose their remaining adherents.

It is distressing to both patients and surgeons when a successful total gastrectomy for cancer of the stomach is marred by such disturbing postoperative symptoms as substernal pain and burning, reflux of intestinal juices into the mouth, and malnutrition. These complaints may be lessened by sleeping in the Fowler position together with frequent feedings of easily digested foods and supplementary medication, but the struggle for existence under these circumstances is most discouraging and difficult. Despite this, there is an increasing advocacy for total gastrectomy in carcinoma of the distal end of the stomach. This is based on a study of the lymph node spread of the disease and involves block removal of the lesion, greater and lesser omentum, the spleen, and perhaps a portion of the pancreas. In considering the merits of this approach a proper balance between the operative mortality and morbidity must be attained. There is very little reason to believe that by removing all of the stomach for cancer of the pylorus, a greater chance for cure is obtained even though there may be submucosal extension. The method of spread to lymph nodes is generally thought to be embolic rather than by permeation; thus, leaving a small portion of the fundus of the stomach but still removing adequately the growth and the lymph drainage area should be consistent with modern concepts for the cure of cancer. The obvious advantages are a lesser operative mortality and the prevention of the more disagreeable postoperative symptoms, because a small gastric reservoir remains and the valvular mechanism of the cardia is left intact. If the location of the tumor forces total gastrectomy and there appears hope for cure, some method of re-establishing intestinal continuity must be devised which will permit the patient to live in comfort. The first requirement in that direction is to suppress any reflux of intestinal juices into the esophagus and second, to create, if at all possible, a storehouse for food. The use of a loop of jejunum with enteroenterostomy should be abandoned just as it has been in cholecystojejunostomy because reflux of juices is not altogether prevented. The principle employed by the Roux Y technique with the blind end of the jejunum isoperistaltic and 12 to 14 inches in length supplies the answer to the problem of esophageal regurgitation but offers no pouch for food storage. Swinging an isolated segment of jejunum of the

same length between esophagus and stomach should be even more effective, as direct contact of food with the duodenal juices may lessen digestive complaints. When the antrum can be preserved, its anastomosis to the esophagus has been suggested. Whether this will prevent irritating esophageal regurgitation remains to be seen. The ingenious use of the cecum and ascending colon with a short piece of ileum attached, the latter sutured to the esophagus, establishes both a storage area and a valve. The magnitude of the operation may limit its application, but the principle is sound. The recently reported substitution of a portion of transverse colon for a stomach is interesting. When utilizing the Roux Y principle or a segment of small intestine between stomach and esophagus, looping the small intestine on itself for a distance and destroying the septum will make a small food pouch.

These more recent methods of establishing intestinal continuity following total gastrectomy indicate a solution for a happier life for those requiring radical surgery. Time alone will determine the best answer.

While the knowledge of the cardioesophageal valve mechanism is not complete, its importance in preventing esophagitis and associated complications is becoming more generally recognized. Surgeons performing operations on the esophagus or stomach should utilize methods which prevent regurgitation of acid peptic juices or intestinal juices into the esophagus. RALPH H. LOE.

SILENT CANCER OF THE LUNG AND TUMORS OF THE CHEST

WITHIN the chest there exists a unique situation for the detection of silent disease. The air in the inflated lungs provides an excellent contrast medium against which the abnormal tissue densities produced by disease are often discernible in the roentgenogram before the lesions have advanced beyond a silent or incipient stage. And certain lesions which are not directly visible may reveal their presence by such secondary evidences as emphysema and atelectasis. This fact led various health conscious institutions and public health agencies to initiate mass chest x-ray surveys to ferret out persons with silent or incipient pulmonary tuberculosis in the campaign to eradicate this communicable disease. For several years city, county, or state-wide mass surveys have been in progress in every state. As a result, the chests of a very large segment of our population have been screened through microfilms. In the surveys reported, the incidence of real and suspected abnormalities of the chest has varied from 0.2 per cent to 5 per cent.

As anticipated, the surveys have brought to light many silent nontuberculous lesions, but the incidence has far exceeded expectations. It is interesting that in addition to the large number of silent pulmonary and mediastinal lesions, these studies revealed many instances of unrecognized abnormalities and diseases of the chest wall and spine, rheumatic and congenital heart diseases, and malformations of the great vessels.

Of utmost importance is the fact that a significant number of the silent lesions are proving to be bronchogenic carcinomas, discovered at a time when the prospect of cure by resection is most favorable. In no other internal concealed organ does there exist a situation which affords such an excellent opportunity for making an early diagnosis of malignant disease. To emphasize the importance of detecting bronchogenic carcinoma in the silent phase, one should recall Overholt's experience. All such survey lesions treated by him were resectable and 75 per cent showed no

evidence of lymphatic spread. In contrast, symptomatic lesions, those which required the attention of a physician, had extended beyond the lung itself in 90 per cent of instances.

From the rather meager evidence available at this time, it is already apparent that the benefits which will be realized by the tumor suspects and nontuberculous survey subjects may exceed those of the tuberculous for whom the surveys were primarily conducted. Many persons are living and well and some presumably cured as a result of the early survey discovery of their bronchogenic cancers. Gratifying as this is, the really significant contribution that the surveys have made to the problem of cancer is the impetus and direction that they have given for an expanded program for the early detection of this disease. It is obvious that surveys that screen individuals at infrequent intervals as at present can detect only a very small percentage of silent bronchogenic carcinomas. For an effective approach to the problem it has been suggested that chest films be made of all persons over 40 years of age every 6 months. The difficulties inherent in this type of program are obvious, but not insurmountable. Efficient plans of operation and a large personnel with administrative know-how have already been developed by survey groups. Agencies and large sums of money are available to implement a program and to carry out the necessary public education. Guiss recently reported that the unit cost of the mass survey conducted in Los Angeles County was $0.754 per person and that it required an expense of $396.00 to discover each chest tumor suspect.

It should be pointed out that the silent benign tumors and other nontuberculous surgical lesions revealed by the survey studies exceed the malignant tumors. The majority of these lesions are included in the tumor suspect group and in most instances should be explored and usually resected for the reasons that (1) they are malignant until proved otherwise by histological examination, (2) certain ones have a propensity to undergo carcinomatous degeneration, (3) many of them will subsequently produce symptoms requiring resection.

It is hoped that this brief discussion of an involved subject may bring increased effective interest in this, one of the largest and most promising fields in the campaign against cancer.

J. Dewey Bisgard.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE fourth edition of *Essentials of Modern Surgery*[1] prepared by Handfield-Jones and Porritt and 12 collaborators which has just been released was surveyed with intense interest. The first edition appeared in 1938 at a time of great stress in England.

In studying this work it becomes quite evident that so far as surgery is concerned an ocean no longer separates Britain from the United States. Few definite differences of opinion as to etiology, pathology, diagnosis, and treatment of surgical diseases are evident.

When the book is studied critically an obvious question arises, the distribution and extent of the subject material. This applies not only to the work under consideration but to other similar works both in America and Britain. As an example, only 18 pages are devoted to diseases of the female genital organs, approximately one and a half pages being allotted to carcinoma of the uterus. Needless to say, the subject is so briefly discussed that its value may be seriously questioned. Certainly it is of no value, practically, to one seeking information on the subject.

The principles of surgery as presented vary but little from American concepts. It is interesting to note that in delineating the treatment of wounds of the hand the author states that if the hand is clean it should be washed thoroughly "but if it is very dirty . . . more harm than good is done by washing." He advocates placing the injured part in a bath of an alcoholic tincture of iodine for 5 minutes. This procedure will be seriously questioned by many American surgeons. Again under treatment of carcinoma of the tongue, in discussing cervical node involvement, it is advocated that when glands are not palpable external irradiation be used. This practice has been deemed futile by American oncologists. No mention is made of the use of isotopes in the diagnosis of thyroid disease and only one phrase of 7 words is devoted to therapy. Mention is made of trauma as a possible etiological factor in chronic mastitis.

Under treatment of cerebral injuries it is stated, "If signs of high intracranial tension appear, lumbar puncture helps especially in the relief of headache." It is the reviewer's opinion that practically all American neurological surgeons condemn such a measure. ACTH and cortisone are not mentioned in the treatment of rheumatoid arthritis.

These differences of opinion are offered not as a criticism of British surgery but to call to the attention of both American and British surgeons that differences of opinion do exist. Difference of opinion may stimulate further study and in the end only good can result.

As a whole the subject matter is very well presented. It does seem that the average British surgeon presents his thoughts in a more fluent and pleasing manner than his American colleague. The chapter on the chest, prepared by Mr. Holmes Sellors, deserves special mention. The subject is so completely covered and the material so concisely arranged and so clearly presented that it is a pleasure to read it. The portion on bronchiectasis is a classic. The chapter on diseases of bone also deserves special mention.

This work can well be another liaison between American and British surgeons. JOHN A. WOLFER.

THE volume entitled *Peptic Ulcer; Clinical Aspects; Diagnosis; Management*[2], edited by David J. Sandweiss, is published under the auspices of the American Gastroenterological Association. It is an authoritative book on all phases of peptic ulcer. In this volume, 77 eminent medical men, well known for their contributions, have reviewed and evaluated the old and new knowledge in their fields. It provides an excellent survey of modern concepts of this disease and a much needed crystallization of current ideas on diagnosis and management. There are chapters on the experimental, diagnostic, clinical, and surgical phases of the ulcer problems designed to meet the need of practicing physicians and surgeons. It emphasizes "the fundamentals which are always fundamental." This brings to the young physician a great deal of mature experience and observation along with up-to-date and new ideas on peptic disease.

There is an extensive bibliography at the end of each chapter and the entire book is indexed by subjects and authors.

This is an outstanding and instructive reference work and is recommended to investigators and clinicians who are attempting to make intelligent clinical interpretations of all phases of peptic ulcer.

ARTHUR J. ATKINSON.

[1] THE ESSENTIALS OF MODERN SURGERY. Edited by R. M. Handfield-Jones, M.C., M.S., F.R.C.S., and Sir Arthur E. Porritt, K.C.M.G., C.B.E., M.A., M.Ch., F.R.C.S. 4th ed. Baltimore: The Williams & Wilkins Co., 1951.

[2] PEPTIC ULCER; CLINICAL ASPECTS; DIAGNOSIS; MANAGEMENT. Edited by David J. Sandweiss, M.D., F.A.C.P. Philadelphia, London: W. B. Saunders Co., 1951.

THE small book *Frontal Lobotomy and Affective Behavior; a Neurophysiological Analysis*[1] is concerned with the current problem of how the patient's affect may be as little changed as possible and still receive benefit by prefrontal lobotomy for intractable pain and various of the psychotic states. It consists of only 4 chapters: a historical background, a discussion of the newer concepts of the functional anatomy of the cerebral cortex, recent behavioral studies in animals, and the results of the various types of surgical attack upon the frontal lobe for the psychoses and intractable pain, together with some critical remarks by the author on these procedures. He points out particularly that the method of Grantham, wherein through a superior approach the medial portion only of the white matter is transected, has favorably impressed him in that it has less undesirable effect upon the patient's normal affect than any of the other procedures and that, furthermore, it is a safe and relatively simple technique. Some interesting remarks are made concerning the effect of lobotomy on sensory phenomena, blood pressure, gastrointestinal functions, and metabolic changes. The book is easy and interesting reading. There is a particularly full and up-to-date list of pertinent references.

JOHN MARTIN.

THE *Festschrift*, presented to Doctor Keeton on the occasion of his retirement after 18 years as head of the Department of Medicine at the University of Illinois College of Medicine, is a tribute to his personal qualities, his influence as a teacher, and his sustained vigor in investigation. *Studies in Medicine*[2] contains, in addition to a biographical sketch and the bibliography of Doctor Keeton, 30 papers written by his friends, associates, and students. Their diversity reflects Doctor Keeton's own wide interests. Their general excellence provides a fitting testimonial, and fulfills the intention of the editorial committee to publish a volume that is a distinct contribution to medical literature.

WALTER H. NADLER.

THE book *Leitfaden der Laparoskopie und Gastroskopie*[3] is a brief but careful manual in the procedures of peritoneoscopy and gastroscopy. It is a text that those already interested in the procedures will want to review. Its aim is to present methods and indications in a fashion that will stimulate interest for wider use of endoscopy as an important additional diagnostic procedure.

The chapters on peritoneoscopy are well written by Kalk. The procedure is carefully explained in detail so that beginners can avoid all mistakes and complications. The normal and pathological features of all the areas accessible to peritoneoscopy are carefully described and illustrated. Kalk prefers his own modification of the instrument. Pneumoperitoneum is induced through a separate needle in the left lower quadrant. For the beginner, the dangers are minimized by using at least 10 patients with ascites before undertaking others. About 2,000 examinations have been made by the author without a death in the entire 25 year period. Needle biopsy is performed under direct vision.

The most important indications for peritoneoscopy, according to the author, are liver disease and the differential diagnosis of intrahepatic and extrahepatic jaundice in which, it is felt, diagnosis can be made in most cases by peritoneoscopy.

Of great interest are the many cases of acute hepatitis in which Kalk has observed the progression of the illness and the gradual development of permanent gross liver damage. A diagram showing the evolution of the disease is used as a reference for the description of the many excellent drawings by Landsberg of views seen through the peritoneoscope.

The section on gastroscopy by Bruhl is a concise but complete description of the best procedure and technique. Gastroscopy is emphasized particularly as an adjunct diagnostic procedure in difficult cases in which x-ray is indefinite or uncertain as to the existence or the nature of a lesion. The author is particularly fond of the Korbsch rigid gastroscope with its optical advantages but advises its use only by the expert gastroscopist after the flexible instrument has been mastered. The optimism regarding the diagnosis of early carcinoma by the gastroscope may be questioned.

The text is well done with highly readable type on excellent paper. Organization of material is simple and clear, and the color pictures are outstanding. It merits an English translation with the original pictures as part of the text.

ARTHUR P. KLOTZ.

THE compilation of material relating to the *Renal Pelvis and Ureter*[4] is presented in a volume of 429 pages. The embryology, gross and microscopic anatomy, and physiology of the kidney and ureter are described and discussed in detail. The pathology and abnormalities of these structures are clearly described and well illustrated. The entire volume contains 264 very instructive illustrations. The various forms of renal pelves and ureters can be appreciated from these illustrations. The author has spent much time on his discussion of the dynamics of the upper urinary tract. The chapter on "Resorption and Absorption in the Upper Urinary Tract" is especially noteworthy because the writer has differentiated meticulously the conditions of pyelocanalicular backflow, pyelosinus transflow, sinolymphatic absorption, and sinovenous ingression.

[1] FRONTAL LOBOTOMY AND AFFECTIVE BEHAVIOR; A NEUROPHYSIOLOGICAL ANALYSIS. By John F. Fulton, M.D. New York: W. W. Norton & Co., 1951.

[2] STUDIES IN MEDICINE; A VOLUME OF PAPERS IN HONOR OF ROBERT WOOD KEETON. Springfield, Ill.: Charles C Thomas, 1951.

[3] LEITFADEN DER LAPAROSKOPIE UND GASTROSKOPIE. By Prof. Dr. Med. H. Kalk, and Dr. Med. Habil. W. Bruehl. Stuttgart: Georg Thieme, 1951.

[4] RENAL PELVIS AND URETER. By Peter A. Narath, M.D., F.I.C.S. New York: Grune & Stratton, 1951.

Anyone who is interested in urography should read this discussion of retrograde and intravenous ureteropyelography. The history, technique, media employed, pitfalls, and the value of each method are well presented. A complete bibliography, index of authors, and index of subjects have been included.

This book is a valuable addition to the surgeon's library. It is especially valuable to urologists, young and old. Dr. Narath is to be complimented and congratulated for this publication.

WILLIAM J. BAKER.

THE book *Lectures on Physiopathology and Clinical Surgery*[1] is an enlargement of and brings up-to-date a previous work which appeared in 1942. Its rewriting has been necessitated because of the great advancement in surgical procedures and the widespread application of modern antibiotic therapeutics. From this viewpoint, each chapter has undergone extensive revision. The selection of subject matter is appreciated; its division, however, is unusual, in that the material is treated under the two general topics of trauma and infection. Inasmuch as this work is intended to be a teaching manual and follows the outline of the prescribed course of instruction, the division of subject matter is understandable. The terseness in which some of the topics are discharged leaves something to be desired. The chapter on tumors, for instance, is allotted only 19 pages, the normal physiochemistry of the human body is dismissed in 30 pages, and many of the subheadings under trauma and infection are of paragraph lengths only. However, here again this approach is definitely of a pedagogic advantage as it permits amplification by the teacher. The language is simple, clear and logical; and the illustrations are informative, in many instances in color. The author definitely has a keen grasp of his subject matter and has presented a work which is highly recommended.

STEPHEN A. ZIEMAN.

THE 294 page book *Angiocardiography*,[2] by Dotter and Steinberg, details the experiences of the authors, concerning a diagnostic procedure (angiocardiography) which they have used for 14 years. They present their experiences concerning the technique, interpretation, indications, and limitations clearly and well. Controversial issues are discussed. The authors state that the usefulness of the book in a large measure rests upon its illustrations. The angiocardiographic reproductions and accompanying labeled tracings are well described and reveal a tremendous amount of thought, skill, and effort given to this one phase of the book.

The attention to detail of techniques in administering the contrast media, the dangers of the method, the mortality, and the x-ray equipment required for the optimum results are well discussed so that those interested can profit by the listed difficulties and successes.

Sixty pages are devoted to study of the normal angiocardiogram. From 2,000 angiocardiograms the most ideal normal results have been selected, traced, and are beautifully reproduced.

The book contains much history, anatomy, physiology, pathology, and therapy. The authors indicate the diagnostic procedures that are preferable to angiocardiography. For example, they state, "The electrocardiogram furnished a more reliable demonstration of early right ventricular enlargement than does angiocardiography." Also, "Contrast visualization is not indicated in the routine investigation of well-established mitral stenosis. It may prove of value in the occasional atypical case of rheumatic heart disease when clinical and laboratory investigation are diagnostically inadequate."

Two hundred and eighty-three pages are devoted to the subject of acquired and congenital intrathoracic pathology, of which 123 pages concern the acquired and congenital lesions of the heart and great vessels.

Dotter and Steinberg state, "Angiocardiography is primarily a method for demonstration of gross anatomic change rather than functional abnormality. The latter may occasionally be inferred when secondary changes are revealed." The indications and contraindications for angiocardiography in patients with varied acquired and congenital lesions of the heart and great vessels are clearly stated and illustrated. This section will be most valuable to the cardiologist and cardiovascular surgeon.

The authors make the following statements concerning mediastinal tumors:

"When facilities allow, angiocardiography should be routinely performed on all cases of mediastinal neoplasms where operation is under consideration" and "Angiocardiography should be an integral part of the routine complete work-up of a suspect primary carcinoma of the lung."

The authors further state that, "In their experience, an angiocardiographic diagnosis of cancer of the lung is possible in approximately 35 per cent of the cases studied. It also indicates as no other preoperative examination can, the anatomic extent of the lesion, enabling the surgeon to plan the most suitable method of approach and informing him as to the otherwise hidden structures of the tumor he plans to attack."

Following each chapter is a bibliography and throughout the book other workers interested in this field are given due credit for their opinions, whether they are in agreement with the authors' views or not.

This book is an extremely valuable contribution. The intrathoracic surgeon, cardiologist, and radiologist particularly will find it stimulating, educational, and of great help in the diagnosis and care of the patient in whom this procedure is indicated.

EGBERT H. FELL.

[1] LECCIONES DE FISIOPATOLOGIA Y CLINICA QUIRURGICA. By Prof. Francisco Martin Lagos. Vol. 1, 2nd ed. Barcelona, Madrid, Lisboa, Valencia: Editorial Cientifico Medica, 1950.

[2] ANGIOCARDIOGRAPHY. By Charles T. Dotter, M.D., and Israel Steinberg, M.D. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1951.

THE principal object of the book *Cancer Cytology of the Uterus Introducing a Concept of Cervical Cell Pathology*[1] by J. Ernest Ayre is to illustrate a graded variety of cytologic phenomena in the development of cancer.

A considerable portion of the contents of the book deals with early anaplastic cells which are discussed in a chapter separate from preinvasive cancer. Here, the author attempts to show that this type of cell is characteristic of the tissue that subsequentlybecomes carcinoma. He believes that the stages in the transition can be identified and followed by serial cell studies. However the stages as shown probably represent only malignant cells as they appear in lesions of varying degrees of differentiation. Confusion is further created by the designation of a group of cells as "precancer cell complex" ("nearo-carcinoma") and in the next sentence by stating that these same cells are characteristic of proved intraepithelial carcinoma. Yet in another place Ayre says that "the precancer cell complex is a stage closely related to the in situ stage." In attempting to show the transition through various stages one case is recorded in detail in which the cells are termed anaplastic, then are shown as "nearo-carcinoma" or precancer type, then as intraepithelial carcinoma, and then in higher power as characteristic of early epidermoid carcinoma. Since the legend to each photomicrograph states the patient is 30 years of age it must be assumed that very little time, if any, elapsed during this sequence of events and the serial preparation of histologic material. It can only be concluded that this case was epidermoid carcinoma when first observed and that chronological transition of cells has not been demonstrated. This analysis is not meant to be facetious but is meant to exemplify the fact that the author and all of us have not yet reached the point where we can recognize and can agree upon the step by step cell changes in the progression from normal squamous epithelium to carcinoma. The failure to prove this point need not detract from the usefulness of the book, the excellent photomicrographs, and the diagnostic procedures described. Certainly the cervical smear method is valuable and when one applies himself to its study as the author has done, he may detect early and significant cell changes that still remain obscure to others.

JOHN I. BREWER.

THE belief that the library of the specialist lacked a comprehensive textbook dealing with a "clinical technique" motivated Georges Portmann, M.D., Dean, and Professor of Otorhinolaryngology, of the University of Bordeaux Medical School to write the volume *Diseases of the Ear, Nose, and Throat.*[2] The stated intent was to describe in detail all the procedures of clinical examination of the ear, nose, and throat patient. The resulting book achieves its purpose in an admirable way.

Professor Portmann believes that the newer diagnostic procedures which have been added to the specialty in modern times in no sense lessen the need of the student, general practitioner, or specialist to develop his powers of observation and his ability to ferret out obvious and latent clinical signs. The physicians power of observation, his diagnostic sense, and his intelligence in taking the history still remain fundamental, and should only be aided and sharpened by modern diagnostic laboratory procedures. Modern training in otolaryngology often devotes too little time to the teaching of clinical diagnosis. Certain factors are in operation that prevent a proper emphasis on the complete and resourceful clinical investigation of the patient. The training program frequently must sacrifice the development of clinical diagnostic technique to the development of surgical skill. It is basically on this premise that the present volume has been conceived and written. The otolaryngologist who recognizes a lack in his ability to conduct a full and varied clinical investigation of the patient will be richly rewarded by a study of this book.

The organization and arrangement of the text is logical. The introduction states the author's method of presentation of the subject material and goes on into a discussion of the fundamental problem of external illumination of the area to be examined. The various modalities of lighting are discussed and illustrated by diagram. Many standard texts omit any reference to proper illumination or the reasons for it; it is attention and devotion to detail that characterize this book.

The textbook proper is developed in 6 sections dealing in turn with the auditory apparatus, the nasal fossae and accessory sinuses, the mouth and pharynx, the larynx, trachea, and bronchi, the esophagus, and laboratory methods in otolaryngology. Each section is developed in four chapters, anatomy, physiology, indirect examination, and direct examination of the organ under consideration. The discussions of the anatomy and physiology are clear, concise, and well illustrated. The real value of the book lies in the chapters describing the indirect and direct methods of clinical examination. Here the reader is given a generous share of the knowledge gained by Portmann from a wide clinical and long teaching experience. Every method of proved value in clinical examination is included and described in detail enough to allow the reader to understand and perform the procedure. Although the material discussed is extensive and detailed the descriptions are not verbose and are easily assimilated. A profusion of diagrams, anatomical drawings, photographs, and photomicrographs point up and clarify the text, and all are particularly well chosen for the intended purpose. In this book of 713 pages there are 666 figures and 11 color plates.

[1] CANCER CYTOLOGY OF THE UTERUS; INTRODUCING A CONCEPT OF CERVICAL CELL PATHOLOGY. By J. Ernest Ayre, M.D. New York: Grune & Stratton, 1951.

[2] DISEASES OF THE EAR, NOSE, AND THROAT; A TEXTBOOK OF CLINICAL AND LABORATORY PROCEDURES. By Georges Portmann, M.D. Translation by Fernand Montreuil, M.D., and Jules G. Waltner, M.D. Baltimore: The Williams & Wilkins Co., 1951.

Each section, chapter, and subject is aptly illustrated, and all figures are large and easily seen in detail. The color plates of normal and pathological conditions are excellent.

This book cannot be criticised by comparison with standard textbooks of otolaryngology. From such a viewpoint there seems, at first reading, to be too much space devoted to the description of clinical tests that vary only slightly in the technique of performance. One hundred and thirty pages are devoted to the indirect examination of cochlear and vestibular function. It can be argued that the length of discussion devoted to testing the vestibular apparatus by use of the Bárány chair is not necessary in these times, but since the book is a text of clinical technique the argument would not be valid. The chapter on the functional examination of the equilibrium is probably the best written and most helpfully illustrated of any in the book.

Most of the tests described in the book could be found by culling the old textbooks, but many of these are no longer available. This textbook presents all of the tests completely, clearly, and interpreted in the light of modern knowledge of physiology and pathology. The book should become a welcome addition to the library of the specialist in otolaryngology, especially of those in the younger age groups. It will be invaluable for the resident in training in otolaryngology, and should be available as a reference book for the intern and the medical student. It will be of great help to the general practitioner. FLETCHER AUSTIN.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for reviews in the interests of our readers and as space permits.

A TEXTBOOK OF CLINICAL NEUROLOGY; WITH AN INTRODUCTION TO THE HISTORY OF NEUROLOGY. By Israel S. Wechsler, M.D. 7th ed. Philadelphia, London: W. B. Saunders Co., 1952.

CALLANDER'S SURGICAL ANATOMY. By Barry J. Anson, M.A., Ph.D. (Med. Sc.), and Walter G. Maddock, M.S., M.D., F.A.C.S. 3rd ed. Philadelphia, London: W. B. Saunders Co., 1952.

BRAIN TUMORS OF CHILDHOOD. By Henry M. Cuneo, M.D., and Carl W. Rand, M.D., Springfield, Ill.: Charles C Thomas, 1952.

CALCULATION OF INDUSTRIAL DISABILITIES OF THE EXTREMETIES. By Carl O. Rice, M.D., M.S., Ph.D., F.A.C.S. Springfield, Ill.: Charles C Thomas, 1952.

ALLGEMAINE UND SPEZIELLE CHIRURGISCHE OPERATIONSLEHRE. Vol. 2, 2nd ed. By Martin Kirschner. Edited by N. Guleke and R. Zenker. Die Eingriffe am Gehirnschadel—Gehirn an der Wirbelsaeule und am Rueckenmark. By Dr. N. Guleke. 2nd ed. Berlin, Goettingen, Heidelberg: Springer-Verlag, 1950.

DAS PHAEOCHROMOZYTOM. By Dr. Heinrich Sack. Stuttgart: Georg Thieme, 1951.

THE PHOTOGRAPHY OF PATIENTS; INCLUDING DISCUSSIONS OF BASIC PHOTOGRAPHY AND OPTICAL PRINCIPLES. By H. Lou Gibson, F.B.P.A., A.P.S.A., Springfield, Ill.: Charles C Thomas, 1952.

TREPHINE TECHNIQUE OF BONE MARROW INFUSIONS AND TISSUE BIOPSIES. By Henry Turkel, B.A., M.A., M.D. 5th ed. Detroit: Gale Printing Co., 1951.

ACTUALIZACIONES DE TEMAS GINECOTOCOLOGICOS. By Prof. Dr. Manuel B. Rodriguez Lopez. 1ª serie. Montevideo: Editorial Ciencia Uruguaya, 1949.

FLUID BALANCE; A CLINICAL MANUAL. By Carl A. Moyer, M.D., Chicago: The Year Book Publishers, Inc., 1952.

THE THYROID. By Thomas Hodge McGavack, B.A., M.D., F.A.C.P. With a Section on Surgery by James M. Winfield, B.A., M.D., F.A.C.S., and Walter L. Mersheimer, B.S., M.D., F.A.C.S., and a Section on History by Dorothy B. Spear, Ph.B., and Thomas Hodge McGavack. St. Louis: The C. V. Mosby Co., 1951.

RUPTURES OF THE ROTATOR CUFF. By H. F. Moseley, M.A., D.M., M.Ch.(Oxon.), F.R.C.S. (Eng. & C.), F.A.C.S. Springfield, Ill.: Charles C Thomas, 1952.

BACKACHE, BIRTH AND FIGURE RELIEF BY SELF-REVOLVING HIPBONES. By Wm. Schoenau. Los Angeles: Wm. Schoenau, 1951.

MONOGRAPHS ON SURGERY—1952. Edited by B. Noland Carter, M.D., Ph.D. Advisory Editors: Gynecology—Joe V. Meigs, M.D., Urology—Charles Huggins, M.D., Orthopedic Surgery—Alfred R. Shands, M.D. Baltimore: The Williams & Wilkins Co., 1952.

LES SYNDROMES DOULOUREUX DE LA REGION EPIGASTRIQUE. By René A. Gutmann. 5th ed., vols. 1 and 2. Paris: G. Doin & Cie, 1951.

THE THORACIC SURGICAL PATIENT; PREOPERATIVE, ANESTHETIC AND POSTOPERATIVE CARE. By Lew A. Hochberg, M.D. Foreword by Frank B. Berry, M.D. New York: Grune & Stratton, 1952.

THE MEDICAL HISTORY OF THE UNION ARMY IN THE CIVIL WAR; DOCTORS IN BLUE. By George Worthington Adams. New York: Henry Schuman, Inc., 1952.

THE DOCTORS JACOBI. By Rhoda Truax. Boston: Little, Brown & Co., 1952.

DAS KLAPP'SCHE KRIECHVERFAHREN. By Dr. Bernhard Klapp. Stuttgart: Georg Thieme Verlag, 1952.

DIE GOETTINGER UNIVERSITAET-FRAUENKLINIK 1751–1951; ENTWICKLUNG DER AELTESTEN DEUTSCHEN FRAUENKLINIK IN ZWEI JAHRHUNDERTEN. By Heinrich Martius. Stuttgart: Georg Thieme Verlag, 1952.

DIE TRANSFUSION VON KONSERVIERTEM BLUT IN DER GEBURTSHLFE UND GYNAEKOLOGIE. By Prof. Dr. H. Schwalm. Stuttgart: Georg Thieme Verlag, 1952.

DER EINFLUSS DES NERVENSYSTEMS AUF BAU UND TAETIGKEIT DER GESCHLECHTSORGANE DES MENSCHEN. By Dr. H. Stieve. Stuttgart: Georg Thieme Verlag, 1952.

CELLULAR CHANGES WITH AGE. By Warren Andrew, Ph.D., M.D. Springfield, Ill.: Charles C Thomas, 1952.

POST-GRADUATE LECTURES ON ORTHOPEDIC DIAGNOSIS AND INDICATIONS. Vol. 3. By Arthur Steindler, M.D., F.A.C.S. Springfield, Ill.: Charles C Thomas, 1952.

AMERICAN COLLEGE OF SURGEONS

INTER-AMERICAN SESSION IN SAO PAULO, BRAZIL, FEBRUARY 10 TO 12, 1953

LEADING South American officials and surgeons will be hosts at the Inter-American Session of the American College of Surgeons in Sao Paulo, Brazil, February 10 to 12, 1953. Meetings of interest to all surgeons including specialists have been scheduled for this second sectional meeting in Latin America, now planned as an annual feature. Dr. Moacyr E. Alvaro, Professor and Head, Department of Ophthalmology, Paulista, Sao Paulo, is Honorary Chairman of the Committee on Local Arrangements. Dr. Benedicto Montenegro, Professor of Surgery, Sao Paulo, and Dr. Euryclides Zerbini, Assistant Professor of Surgical Clinic and Assistant, First Surgical Clinic, Sao Paulo, will serve as Secretary on the same committee.

This meeting has been scheduled for midweek, so that surgeons may use the preceding or following weekend for vacation purposes. The climate in Brazil is pleasant during February, nearby resorts attractive for vacation purposes, and transportation facilities excellent. Forty planes a day leave for nearby Rio de Janeiro.

Brazilian officials will formally open the meeting Monday evening, February 9, at the Municipal Library. Tuesday and Wednesday sessions will be held at the beautiful new building of the Paulista Medical Association. The third day will be set aside for specialty groups, with lectures, panel discussions, hospital clinics, and demonstrations in the surgical specialties.

The surgical program will begin Tuesday morning, February 10, at 10 a.m. with a discussion on treatment of megacolon, followed by a symposium on peripheral vascular diseases. Papers to be presented at this symposium will include "Sequelae of Thrombophlebitis," "Sympathectomy in the Treatment of Raynaud's Disease," and "Surgical Treatment of Aneurysm of Peripheral Arteries." Afternoon sessions will include a panel discussion on portal hypertension and surgery of acquired heart diseases. Activities of the American College of Surgeons will be discussed by prominent speakers at the dinner meeting Tuesday evening at 6 o'clock. A symposium on the management of major emergencies will follow the dinner meeting, featuring the topics, "Emergency Treatment of Burns," "Cranial Cephalic Injuries," "Resuscitation," and "Anesthesia in Emergency Cases."

On the second morning at 9:30 a symposium on cancer will be held. Papers on "Operability and Surgical Results of Cancer of the Lung," "Treatment of Esophageal Cancer," "Selection of Patients for Surgical Treatment of Breast Cancer," and "Surgical Treatment of Cancer of the Rectum" will be presented. Afternoon meetings will feature a panel discussion on complications of a peptic ulcer and a symposium on gynecology, at which the following papers will be heard: "Pelvic Lymphadenectomy in Cancer of the Cervix," "Total Versus Subtotal Hysterectomy," "Allergy in Gynecology," and "Surgical Treatment of Sterility."

Medical motion pictures will be featured both days. Hospital clinics will be held on the third day.

Leading North American and South American surgeons will speak on the several sessions.